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OXIDATIVE PROPERTIES OF THE IRON - THYMINE-1-ACETIC ACID - HYDROGEN PEROXIDE CATALYTIC SYSTEM

Tesi di Laurea Sperimentale

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Abbreviations

(Ac) = acetate, CH_3COO^-

CAN = ammonium ceric nitrate

DFT = density functional theory

EtOAc = Ethyl acetate

GC-MS = Gas Chromatography- Mass Spectroscopy

MeCN = acetonitrile

MeOH = methanol

NHS = N-halosuccinimide

Nu = nucleophile

O/N = overnight

phen = 1,10-phenantroline

PTC = phase transfer catalyst

RT = room temperature

TBHP = tert-butyl hydroperoxide

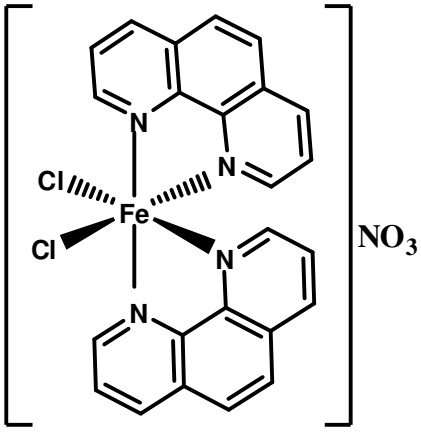
THA = thymine-1-acetic acid

X = halogen

Abstract

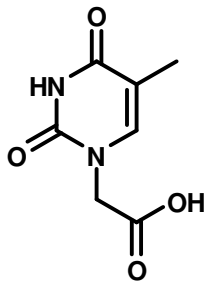
The oxidation of alcohols and olefins is a pivotal reaction in organic synthesis. However, traditional oxidants are toxic and they often release a considerable amounts of by-products. Here, two Iron^{III}-based systems are shown as oxidative catalyst, working in mild conditions with hydrogen peroxide as primary oxidant.

An efficient catalytic system for the selective oxidation of several alcohols to their corresponding aldehydes and ketones was developed and characterized, $[Fe(phen)_2Cl_2]NO_3$ (phen = 1,10-Phenantroline). It was demonstrated that the adoption of a buffered aqueous solution is of crucial importance to ensure both considerable activity and selectivity.



The Iron - Thymine-1-acetic acid in-situ complex was studied as catalyst in alcohol oxidations and C-H oxidative functionalization, involving hydrogen peroxide as primary oxidant in mild reaction conditions. The catalytic ability in alcohol oxidations was investigated by Density Functional Theory calculations, however the catalyst still has uncertain structure. The system shows satisfactory activity in alcohol oxidation and aliphatic rings functionalization.

The Fe-THA system was studied in cyclohexene oxidation and oxidative halogenations. Halide salts such as NBu_4X and NH_4X were introduced in the catalytic system as halogens source to obtain cyclohexene derivatives such as halohydrins, important synthetic intermediates.



Thymine acetic acid
THA

The purpose of this dissertation is to contribute in testing new catalytic systems for alcohol oxidations and C-H functionalization. In particular, most of the efforts in this work focus on studying the Iron - Thymine-1-acetic acid (THA) systems as non-heme oxidative model, which present:

- an iron metal centre(s) as a coordinative active site
- hydrogen peroxide as a primary oxidant
- THA as an eco-friendly, biocompatible, low cost coordinating ligand

Abstract

L'obiettivo di questa dissertazione è di contribuire nello sviluppo di nuovi sistemi catalitici per l'ossidazione degli alcol e per la funzionalizzazione C-H, con sistemi aventi Ferro quale centro metallico attivo e perossido di idrogeno come ossidante primario. L'ossidazione di alcol ed olefine è una reazione centrale nella sintesi organica. Tuttavia, gli ossidanti tradizionali sono tossici e spesso rilasciano quantità rilevanti di sottoprodotti. Con il proposito di sviluppare processi più ecosostenibili, sono presentati i risultati di due catalizzatori di ossidazione a base di $Ferro^{III}$, in condizioni di reazione blande (T=50-60 °C, P= 1 atm., t=30-120 min) con perossido di idrogeno come ossidante primario. Il complesso $[Fe(phen)_2Cl_2]NO_3$ (phen = 1,10-Fenantrolina), sintetizzato e caratterizzato, si è dimostrato un efficiente catalizzatore di ossidazione selettiva di alcoli di diverse classi nei corrispondenti aldeidi e chetoni. L'utilizzo di un ambiente acquoso tamponato (HCl, pH=1), si è rivelato di cruciale importanza per assicurare la considerevole attività e selettività.

Le indagini più recenti si sono dirette allo studio del sistema Ferro (III)– Timina-1-acido acetico (THA) per soddisfare i seguenti requisiti:

- Un centro metallico come sito di coordinazione attivo
- Perossido di idrogeno come ossidante primario
- THA come legante di coordinazione eco- e bio-compatibile a basso costo
- Blande condizioni di ossidazione

L'addotto Ferro – Timina-1-acido acetico è stato studiato come catalizzatore nelle ossidazioni di alcoli, nella funzionalizzazione ossidativa di legami C-H di anelli alifatici e nell'alogenazione ossidativa del cicloesene in presenza di $(NBu_4)X$ e $(NH_4)X$ ($X=Cl^-$, Br^-). Il meccanismo della reazione di ossidazione degli alcoli è stato investigato attraverso calcoli DFT (Density Functional Theory), ottenendo risultati preliminari.

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1) Introduction

The oxidation of alcohols to aldehydes and ketones is one of the most common organic transformation, since those compounds are useful starting materials both in petrochemical industry and in the fine chemicals sector.[1]

These transformations are of basic relevance for obtaining chemicals from oil and gas-base feedstock such as benzene, toluene, methanol and ethene. The choice of the primary oxidant, the catalyst and the physical phase deserve great attention, also to ensure the economic sustainability of the process. Industrially the adoption of catalytic gas- or liquid-state processes is about half to half, involving heterogeneous or homogeneous catalyst.

Although the advantages concerning work-up operations provided by the adoption of an heterogeneous catalytic system, often the choice fall on the homogeneous solution.[2]

The implication of solubilised metal salts or complexes, provide better conversion rate and great selectivity control due to ligands-fine-tuning. Furthermore, bio-catalysts needs to be mentioned as nature-inspired new catalysts, mainly concerning oxidations of aromatic side chains. In the presence of side products, the key role of the catalyst is to provide the selectivity.

Traditionally, the use of stoichiometric oxidants, such as HNO_3, $HClO_4$ or $KMnO_4$, with extensive waste generation, was widely accepted. Nowadays, in view of increasingly stringent environmental regulations, the use of these oxidants is tolerated exclusively for drugs and fine chemicals, by virtue of the high value and the relatively small quantities involved. In the petrochemical industry most of the catalytic cycles involve the use of molecular oxygen as oxidant, mainly for economic reasons. The catalyst has a key role in permitting the spin-forbidden cross-step of the molecular oxygen, thus reducing the energy gap between triplet and singlet excited state. A free radical pathway is the most common way to overcome the activation energy barrier. An organic singlet state molecule reacts with the $^3O_2$ to afford two $^1O^*$ free radicals (Fig.1). The spin-allowed path is strongly endothermic and may occurs at moderate temperature in the case of stabilized radical intermediates (i.e. hydroquinones or reduced flavins).

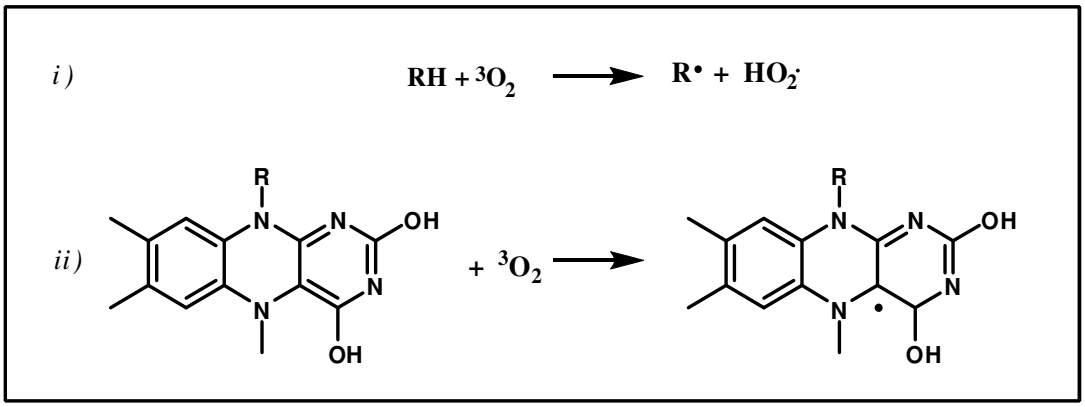


Fig. 1) Molecular oxygen free-radicals generation

An alternative path is to introduce a paramagnetic transition metal ion which allows the formation of a superoxo-metal complex and with subsequent generation of oxo-metal species via inter- or intra-molecular electron-transfer. However the mechanism interpretation is still ambiguous.

A different synthetic route involves the use of reduced forms of dioxygen as hydrogen peroxide, which represents a valid green alternative as primary oxidant, affording just water as co-product. However, there is a large number of single oxygen donors, like organic peroxides ROOH (R: tert-butyl or cumene), which are suitable for industrial oxidations. In the contest of environmental acceptability, criteria as active oxygen weight percentage (Table 1) and the type of co-products have to be considered. Based on these remarks, hydrogen peroxide remains the best option. In some cases co-products recycling with H_2O_2 is a winning strategy for improving the eco-sustainability of the entire process, although this extra step necessarily implies higher investments.

Oxygen donor	Active oxygen %	Coproduct
H_2O_2	47.0 (14.1)	H_2O
N_2O	36.4	N_2
O_3	33.3	O_2
CH_3CO_3H	21.1	CH_3CO_2H
tert-BuO_2H	17.8	tert-BuOH
HNO_3	25.4	NO_x

Table 1) Active oxygen percentage of common oxidant[2]

Value in parenthesis refers to 30% aqueous H_2O_2

Basically, all oxidations follow homolytic or heterolytic mechanism. The homolytic mechanism is considered to be autocatalytic, as the primary oxidant reacts with the organic substrate to promote a radical chain propagation.

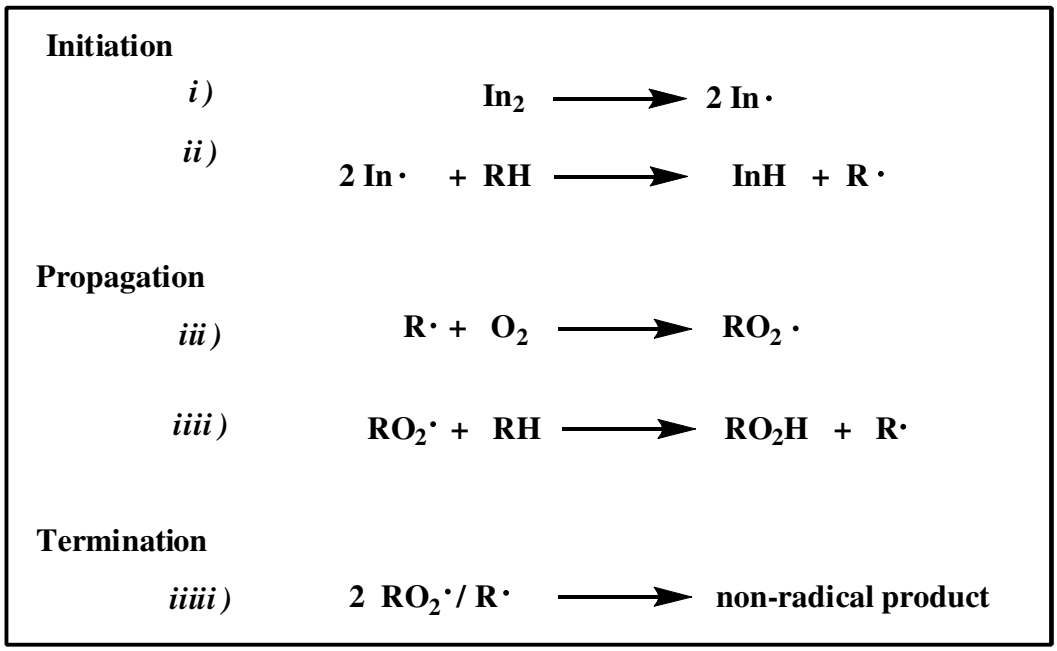


Fig. 2) Radical chain propagation

An oxidized metal catalyst works as electron transfer agent in a direct one-electron oxidation (i.e. p-xilene oxidation) (Fig. 3).

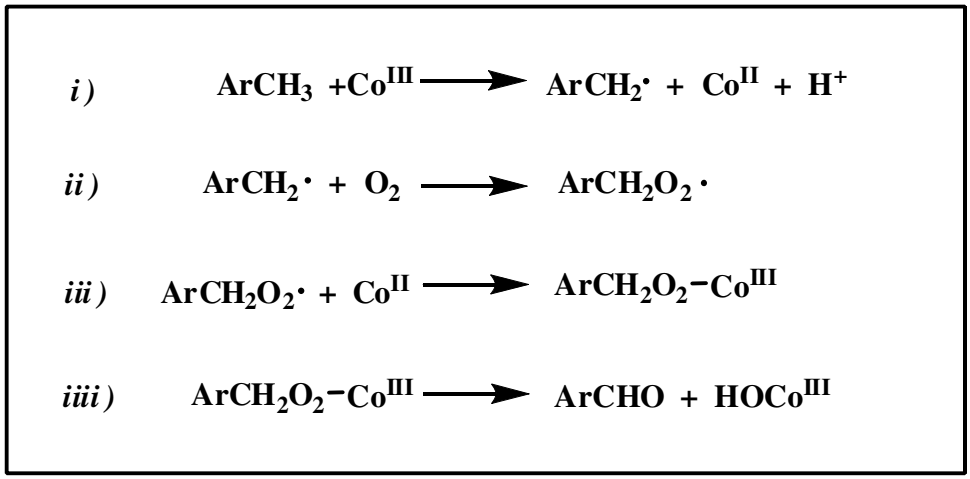


Fig. 3) Metal catalyzed one electron transfer

On the other side, an heterolytic pathway is preferred when the substrate coordinated to the metal, undergoes a two-electron oxidation by action of high valent metal ion, which is subsequently restored to the original form by molecular oxygen (Fig. 4, i-ii).[3] Reduced form of dioxygen follow the general single oxygen donation reaction scheme (Fig. 4, iii).

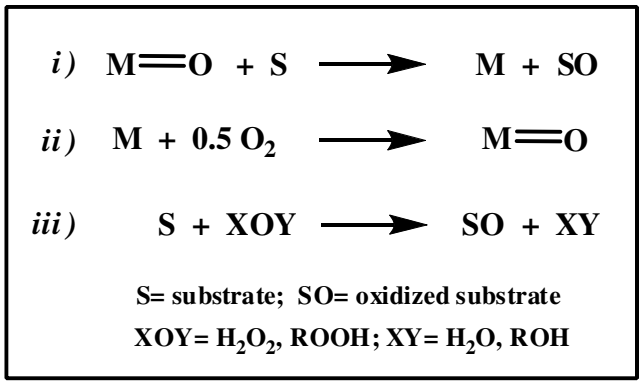


Fig. 4) Metal catalyzed oxidations

As described above, the possible competition of metal-catalyzed homolytic decomposition, leading to free radical oxidation pathways is a disadvantage.

Two heterolytic oxygen-transfer pathways can be identified (Fig. 5), on the base of active metal-oxidant intermediates. Generally a high valent peroxometal complexes are formed by using early transition metals (Mo, W, Re, V, Ti, Zr), whereas with late transition metals (Ru, Os) or first row metals (Cr, Mn, Fe) oxo-metal complexes are involved.

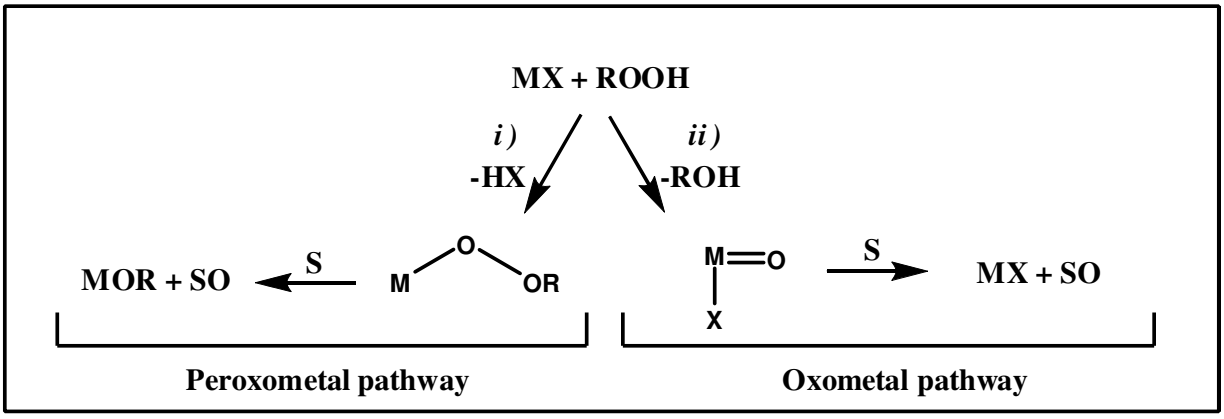


Fig. 5) Heterolytic oxygen transfer paths

1.1) Iron in oxidations

Iron is the fourth most abundant element in the earth's crust[4] and is probably one of the most important and versatile redox center for life and natural transformation processes[5]. Iron represents an ideal metal for the development of environmentally friendly catalyst family, because of the availability, low price and toxicity. However, the majority of the known iron-catalyzed reactions are limited in the scope and not available for practical applications. Thus, the use of iron as catalyst is so far underdeveloped.

The advantages provided by iron catalysis justify a significant increase in research[6] in this field in the mid-term future for ultimately afford industrial applications. Main research topics will be focused on ligand design and relationship between structure and reaction mechanism.

Based on these remarks, recently a large number of iron containing systems have been developed for hydroxylation[7], epoxydation[8], alcohols oxidation[9], sulphide oxidation[10], cross-coupling reactions[11], heterolytic RO-OH bond cleavage[12], hydroamination[13], allylic alkylation or amination[14]. Nevertheless, the intrinsic problem of non-selective radical side-reactions in the redox chemistry of iron has not been totally solved.

The mixture of Fe^{2+} salts and H_2O_2 as oxidative agent is known since the 19th century as Fenton's reagent[15], all analogous reactions involving a metal complex and peroxide are named Fenton-like reactions.

The classical mechanism implies a radical path. The oxidative ability is due to the presence of hydroxyl free radicals[16] (OH●) generated from the peroxide metal-catalyzed dissociation (Fig. 6). The hydroxyl radical is highly reactive and it tends to react itself with the organic substrate; it is a potent H-atom abstractor, since the energy of the O-H bond of water is 109.6 kcal/mol, stronger than most of C-H bonds. On one hand this chemistry is superb for disinfecting applications but on the other hand it is not suitable for chemical technologies because it leans to non-selective transformations and degradations.

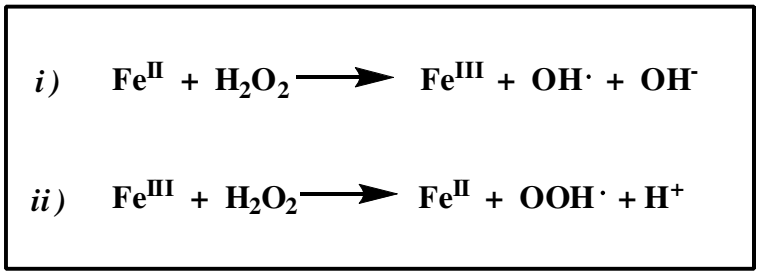


Fig. 6) Hydrogen peroxide dissociation

The second mechanism is the "oxygenated Fenton chemistry", in which the metal ion abstracts an oxygen from hydrogen peroxide forming a two electrons oxidized oxo-metal species and water (Fig. 7).

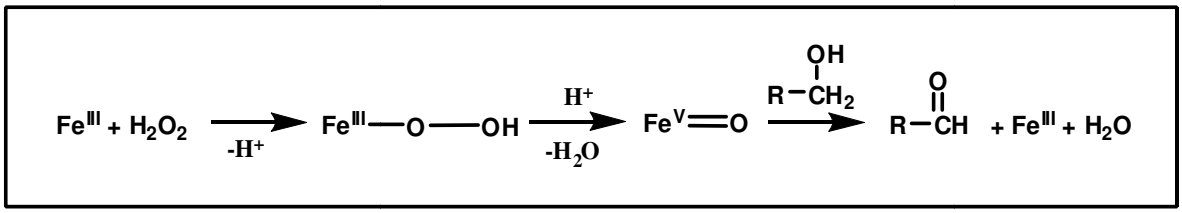
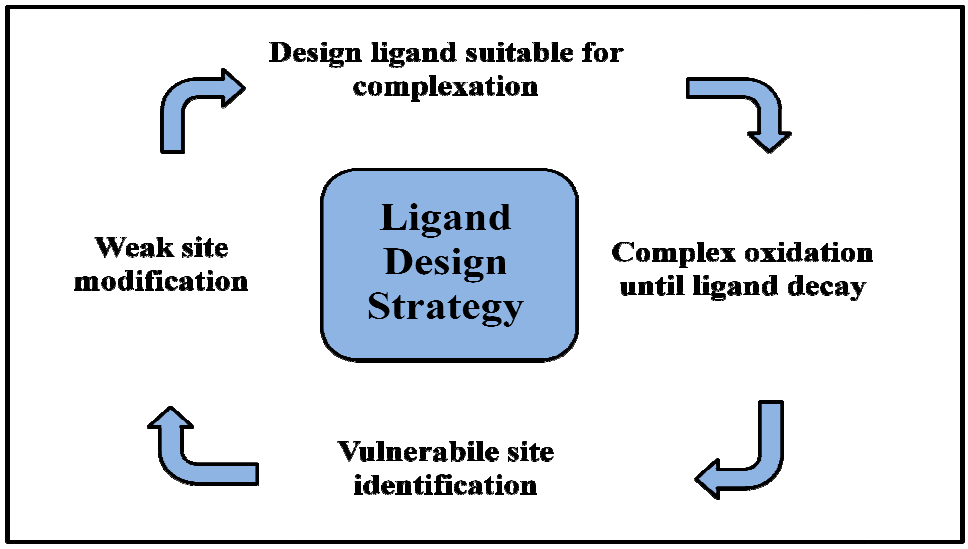


Fig. 7) Oxo-metal species involvement

Unfortunately, after a century of further researches the detailed mechanism is still ambiguous[17], and there is no complete evidence to exclude a certain involvement of both oxo-metal and radical paths. The results published by independent authors, often arising from experiments performed in different reaction conditions, clearly indicate that the system is very sensitive towards solvent, type of ligands, catalyst and oxidant ratio.

The ligand plays the important role of binding the metal ion and help the two electrons oxidation to give oxo-metal formation instead of generation of radical pathways[18]. Iron readily develop radical chemistry thus the coordinated ligand has also to be resistant enough to prevent further oxidation and avoid lack in selectivity.

A successful strategy to develop valid ligands for oxidative catalysis was brilliantly proposed by Collins's group[19], whose efforts are focused both on ligand stability and design weakness (Scheme 1).



Scheme 1) Collin's ligands design strategy

Recently, the biomimetic approach in ligand design is a common hype. The aim is mimic the reactivity of natural enzymes in metal complex catalyzed transformations. The most studied family of oxidase is represented by Cytochrome P450. The oxidative ability is mainly ascribed to the presence of the porphyrin group as enzymatic active site. Basically it is formed by four pyrrole rings bonded together via allylic bridges. When an iron atom is coordinated by the porphyrin group it forms the active heme centre (or haem),(Fig.8).

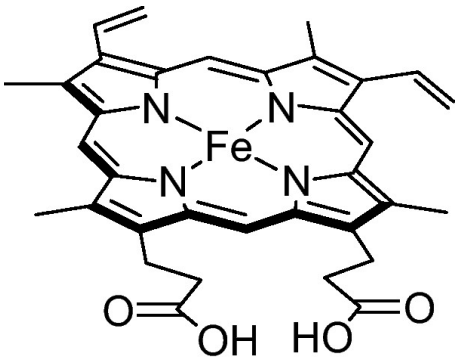


Fig. 8) Porphyrin group

The oxidation key intermediates of many heme and non-heme iron complexes have been widely studied, hence we dispose of a large background data[20]. It has been widely demonstrated the feasibility of bio-inspired catalyst in chemo-, regio- and/or stereo-selective oxidation[21], it is generally accepted that the oxo-iron (V) intermediate would plays the key role, whereas the generation of radical and secondary products is related to the presence of iron (IV). However these systems may be very expensive and not really suitable for industrial application.

The purpose of this dissertation is to contribute in testing new catalytic systems for alcohols oxidation and C-H functionalization. In particular, most of the efforts are focusing in studying catalytic systems which present:

- an iron metal centre as a coordinative active site
- hydrogen peroxide as a primary oxidant
- thymine as a low cost and eco-friendly ligand

2) Alcohol oxidation

Alcohol oxidation catalyzed by iron complexes have been already investigate and a large number of options is available.[22] However a general method has not been discovered and improvements are still desired. The model substrate selected for this study is benzyl alcohol (b), similar to veratryl alcohol (3,4-Dimetoxybenzyl alcohol, Fig. 1 , a) a model molecule for lignin, a wood component which is oxidatively degraded during pulp bleaching[23]. The develop of a new catalytic system in this direction could be of interest for fine chemicals industry as well for pulp bleaching processes. Benzyl alcohol is also a molecule easy to be oxidized, since the methylene group is activated by the aromatic ring. The target is to get selective conversion to benzaldehyde (Fig. 1, c) avoiding the formation of benzoic acid (Fig. 1, d).

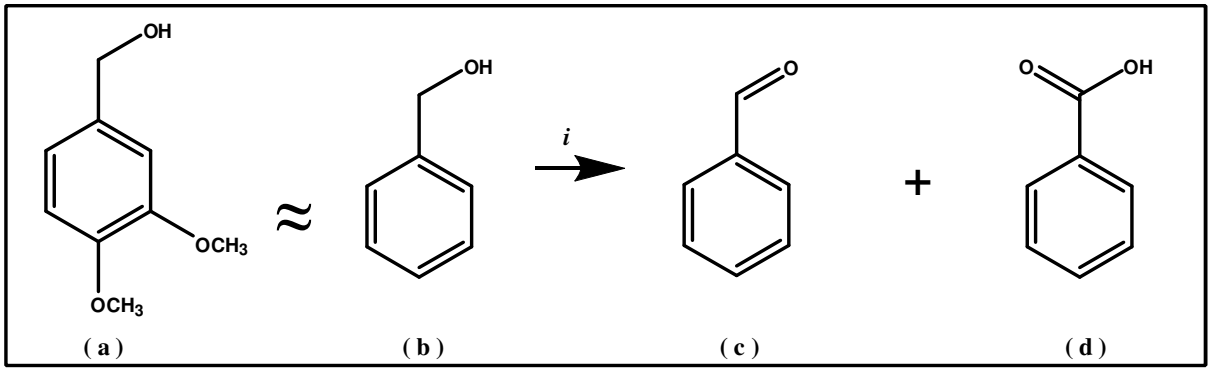


Fig. 1) Benzyl alcohol oxidation

2.1) $[Fe(phen)_2Cl_2]NO_3$ complex

The purpose of this section was to prepare the $[Fe(phen)_2Cl_2]NO_3$ complex and use it as oxidation catalyst in optimized reaction conditions. Phenantroline is known to be an efficient bidentate ligand for a large variety of transition metal ions. It is often adopted in OLED synthesis[24] and combined with iron it forms the ferroin cation $[Fe(phen)_3]^{2+}$ which it is used in the photometric determination of Fe^{II}.[25] The Fe-phen coordination structure is similar to many tri- and tetra-dentate non-heme ligands, but phenantroline is cheaper and commercially available.

The hexa-coordinate iron complex (1) (Fig. 2) was prepared from $FeCl_3$ and 1,10-phenantroline in acetic acid aqueous solutions at room temperature and in presence of ammonium Ceric nitrate $[(NH_4)_2Ce^{IV}(NO_3)_6]$.[26] The role of the Ceric salt is to keep the

metal centre in the oxidized state. The complex is sufficiently stable in air and in presence of moisture to be handled without particular precautions, it is soluble in many solvents such as methanol, ethanol, dichloromethane, acetonitrile, dimethylformamide and dimethyl sulfoxide. The synthesized complex permits stabilization of Iron(III) which allows us to speculate an oxo-metal intermediate Fe(V) as a crucial step in the oxidative catalysis, similarly to what proposed in literature for non-heme complexes.

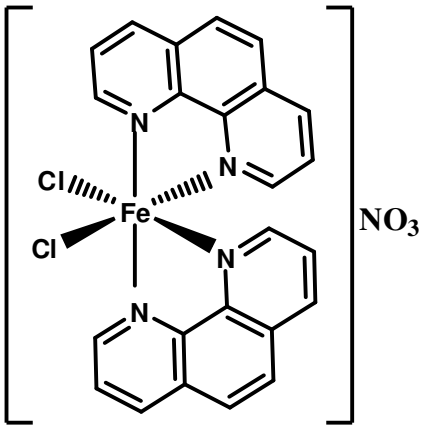


Fig. 2) $[Fe(phen)_2Cl_2]NO_3$ Complex (1)

Acetonitrile solvent was chosen as a solvent because it has good coordinating features, great polarity and non-protic character. Reaction conditions were optimized modulating temperature, amount of catalyst, amount of oxidant and time of addition. The best result was achieved using 5 mol-% of catalyst in MeCN at 55°C, with 2.2 eq of H_2O_2 (33 $\%_{m/v}$) added in 1 h to the alcohol. This outcome results in 77% of alcohol conversion and 58% of selectivity in aldehyde in a total reaction time of 2 h.

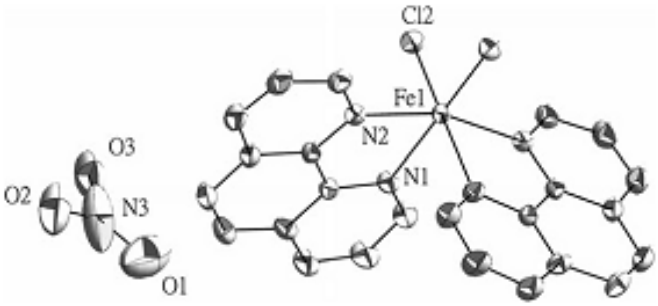


Fig. 3) X-ray crystallography of $[Fe(phen)_2Cl_2]NO_3$ [26]

In 2008 Beller and co-workers[27] explored the influence of the proton concentration in a Fe-catalyzed oxidative system with benzyl alcohol as substrate, solvent free and H_2O_2 as primary oxidant. They discovered that a strictly pH control of the reaction solution

around pH=1 is of fundamental importance for ensure good catalytic activity and selectivity via the proposed oxo-iron intermediate. Deviations (ΔpH = 0.1) doesn't affect the selectivity, but the conversion decreases considerably at higher pH, suggesting a direct correlation between conversion and the acidity of the environment. Thus the proton availability seems to control the choice between the two mechanistic routes (Fig. 4) and only the acid concentration is the crucial factor, independently from the buffer composition.

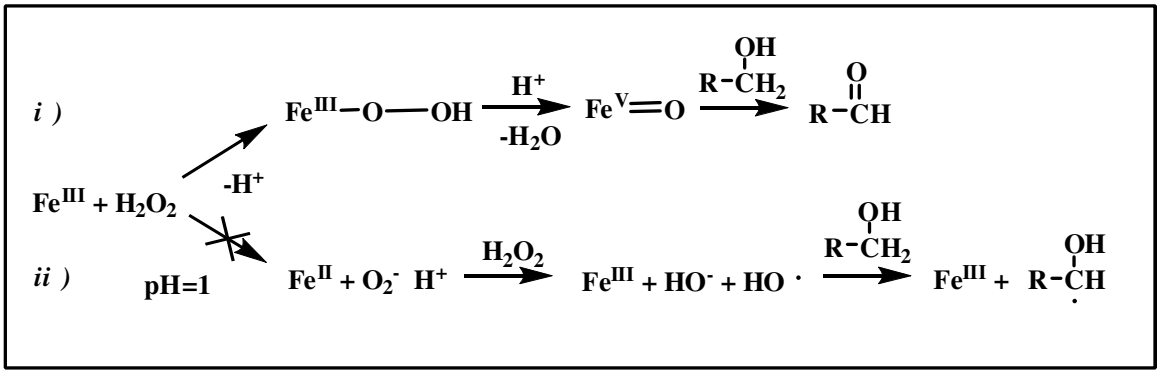


Fig. 4) Acidity effect on oxidative paths

Kinetic studies demonstrate that the C-H hydrogen abstraction is the rate determining step in benzyl alcohol oxidation.

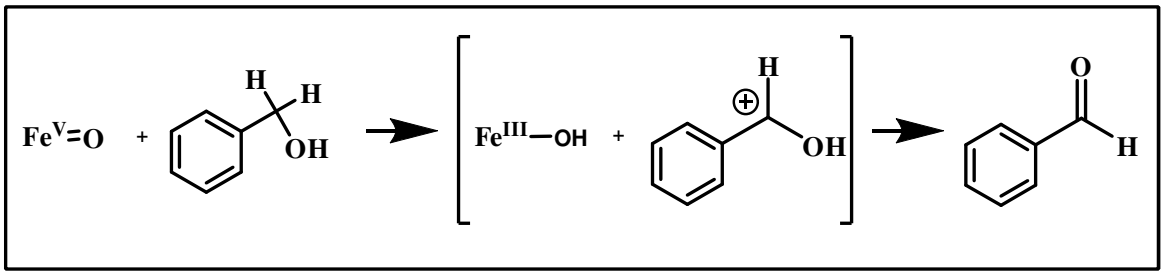


Fig. 5) Proposed mechanism for benzyl alcohol oxidation to benzaldehyde

Inspired by this study, we introduced an aqueous environment in this work, replacing MeCN with a commercial HCl buffer solution pH=1. The best conditions were found to be with 1.5 mol- % of catalyst, solvent free at 55 °C, with 2.2 eq of H_2O_2 (33 $\%_{m/v}$) added in 10 min and a total reaction time of 30 min. Benzyl alcohol was almost fully converted (97 %) with 98 % of selectivity in aldehyde.

	Benzyl alcohol	Benzaldehyde	Benzoic acid
MeCN 2h - 55°C - 5 mol-% Cat	23	45	32
Buffer HCl pH=1 30min - 55°C - 1.5 mol-% Cat	3	95	2
Buffer HCl pH=1 30min - 55 °C – No Cat	98	2	0

Table 1) Benzyl alcohol oxidation GC-MS % results

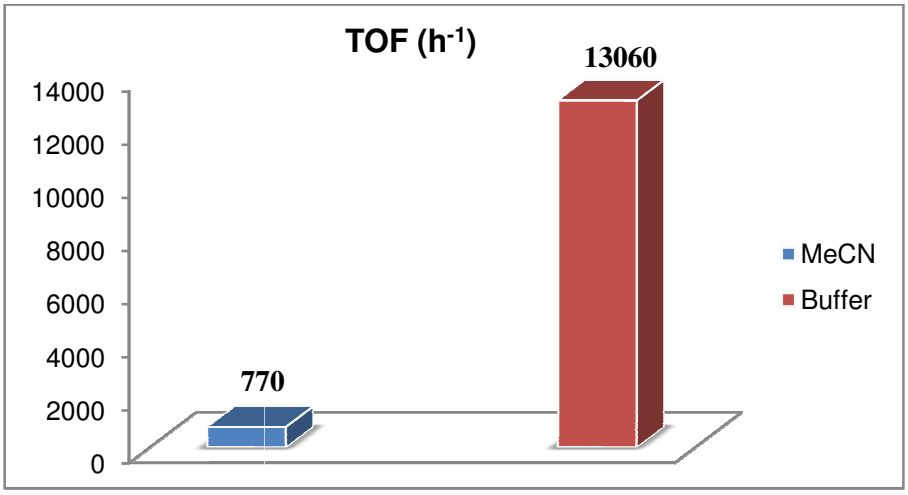


Fig. 6) Turnover frequency comparison

These results are in accordance with Beller's studies[26], confirming that the pH is a key factor in iron catalyzed oxidative systems for enhance H_2O_2 activity and ensure the selectivity towards aldehyde. The influence of the proton availability on the catalyst activity is underlined by the comparison between the catalyst turnover number shown in the two different conditions (Fig. 6).

The efficiency of the catalyst was studied by using structurally diverse primary and secondary alcohols under the optimized reaction conditions (Table 2).

α,β-Unsaturated primary alcohols, such as benzylic and allylic alcohols, can be selectively oxidized to the corresponding aldehydes in excellent yield (entries 1, 10). Similarly, α,β-saturated primary alcohols such as 1-octanol and 1-undecanol can be transformed in their corresponding aldehydes in moderate yield (62-65%; entries 2, 3). It is worth noting that these results encouraged more studies on secondary alcohols oxidation. Secondary aliphatic alcohols were oxidized selectively to the corresponding

ketones in excellent yields (70-96%; entries 4-9). Not only α,β-unsaturated secondary alcohols such as 1-phenylpropanol (95%; entry 4) and 1-phenylethanol (96%; entry 5) were easily converted but also sterically hindered secondary alcohols such as those in entries 6 and 7, were converted to a moderate degree. The catalyst shows an interesting regioselectivity for a vicinal diol such as 1-phenyl-1-ethanediol (entry 12). Only the secondary hydroxyl group is oxidized, which leaves the primary alcohol function intact. 2-Hydroxyacetophenone was observed as the main product (75%) and only a small amount of mandelic acid was obtained (15%). In general, 2-thiophenemethanol (entry 13) is considered to be a difficult substrate for most oxidation systems that involve transition metals because of their strong coordinative ability with the sulfide group. 2-Thiophenemethanol was smoothly oxidized to the corresponding acid with high yield and selectivity (90%; 99%), it is worth noting that the sulfide group, susceptible to oxidation, remains here unreacted. The large number of substrates efficiently transformed demonstrate the great potential of this catalyst in alcohol oxidations.

The introduction of the greener environment (as specified above) allows us to:

- decrease the catalyst amount
- achieve better reaction performance
- decrease dramatically the reaction time and tar formation, due mainly to radical phenomenon

All the results collected during this work were published on the European Journal of Inorganic Chemistry in 2012.[26]

Unfortunately some catalyst degradation was observed during the reaction and phenantroline is toxic and dangerous for the aqueous environment, thus alternative solutions for up-scaled applications are desirable.

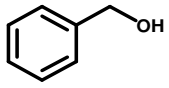
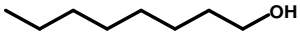
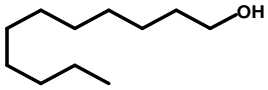
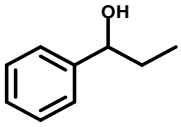
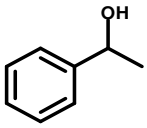
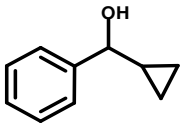
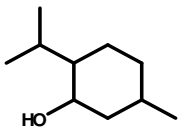
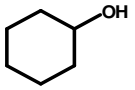
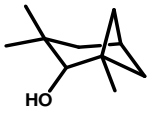
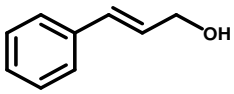
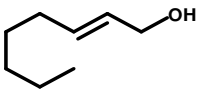
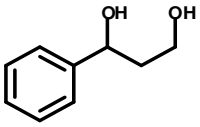
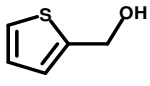
Entry	Substrate	t (min)	Yield %	Selectivity %
1		30	97	98
2		60	65	90
3		120	62	91
4		30	95	99
5		60	96	99
6		60	93	99
7		120	65	99
8		120	73	99
9		120	69	99
10		60	91	83
11		120	35	99
12		60	81	75
13		30	90	99

Table 2) Oxidation of various alcohols into aldehydes and ketones in standard reaction conditions. Conversion and yield were determined by GC-MS and ^{1}H NMR.

2.2) Iron-Thymine-1-acetic acid in-situ complex

In the last few years different flavins[28] and its derivatives were reported to be active as organocatalysts or ligands for organometallic oxidative systems.

In 2010 Repo and co-workers[29] reported the use of the in-situ generated $FeCl_3$-THA catalyst for primary and secondary alcohols oxidation to the corresponding aldehydes, ketones and acids, involving tert-butyl hydroperoxide as primary oxidant. Thymine-1-acetic acid ((5-Methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl) acetic acid; Fig. 7, THA) is an highly polar aromatic molecule soluble in water, MeOH and MeCN; THA is structurally a pyrimidine derivative, comparable to flavin but less costly, commercially available and eco-compatible.

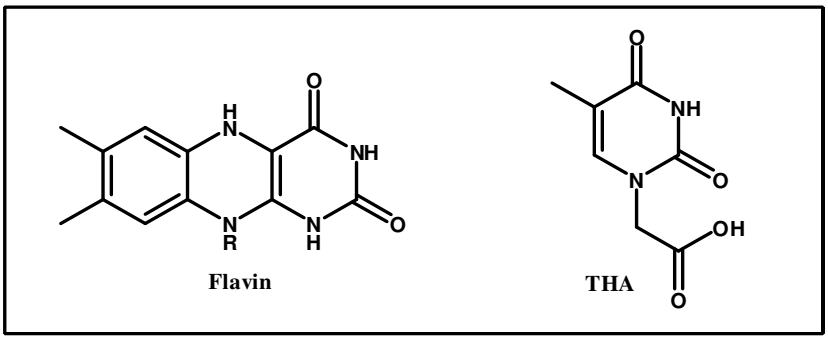


Fig. 7) Structural analogies

In line the results achieved by pH control, we decided to adopt a greener system by substituting TBHP with H_2O_2 and carrying out the oxidations in aqueous buffer (pH=1). The highest activity is observed when THA is added two-fold with respect to the metal . The increase of the ligand/ Fe ratio does not improve the catalyst performances. Further investigations about the solvated complex or attempts to isolate the intermediate species were not carried out during the screening of the oxidative system.

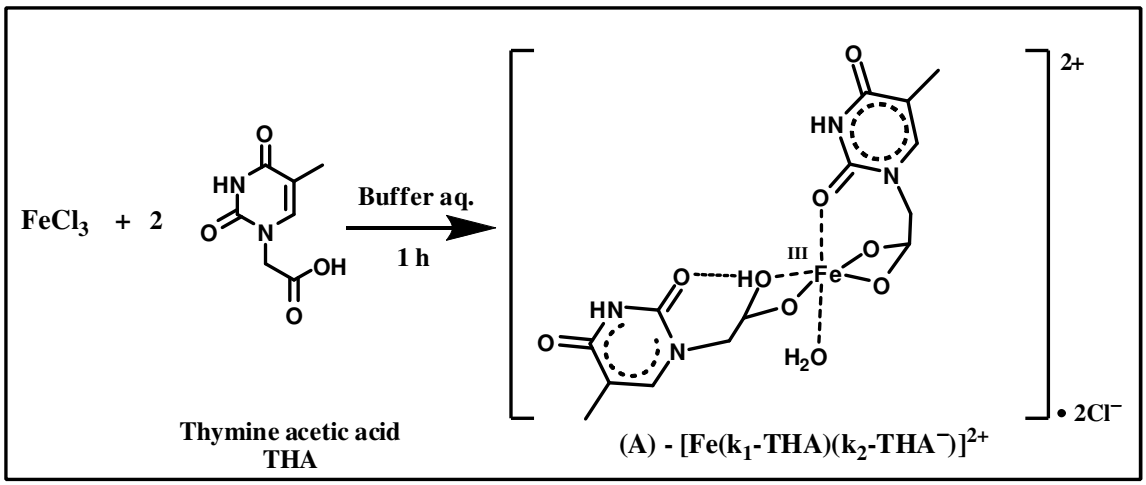


Fig. 8) Proposed iron coordinative sphere for the Fe-THA aggregate (A)

The activity of the Fe-THA as oxidation catalyst was tested in benzyl alcohol oxidation. The metal salt and THA were stirred in the buffer solution, allowing the formation of the in-situ catalyst, which shows the best performance after 1 h. Afterwards 1mmol of benzyl alcohol was added and the reaction was started by adding the oxidant via syringe pump. The results obtained confirm the crucial influence of the pH controlled environment in enhance the peroxide activity. An advantage of the in-situ generated catalytic system is the absence of complex preparation and purification procedures. Moreover, under the reaction conditions there is no evidence of ligand degradation due to double bond oxidation or acid group decarboxylation. This observation allows us to hypothesize the recyclability of the aqueous catalytic system.

	Benzyl alcohol	**Benzaldehyde**	**Benzoic acid**
$FeCl_3$-THA / H_2O_2 30 min- 55°C - 3 mol-% Cat	**12**	**69**	**19**
$FeCl_3$-THA / TBHP 30min - 55°C – 3 mol-% Cat	**93**	**7**	**0**
Buffer HCl pH=1 30min - 55 °C – No Cat	**98**	**2**	**0**

Table 3) Benzyl alcohol oxidation GC-MS % results

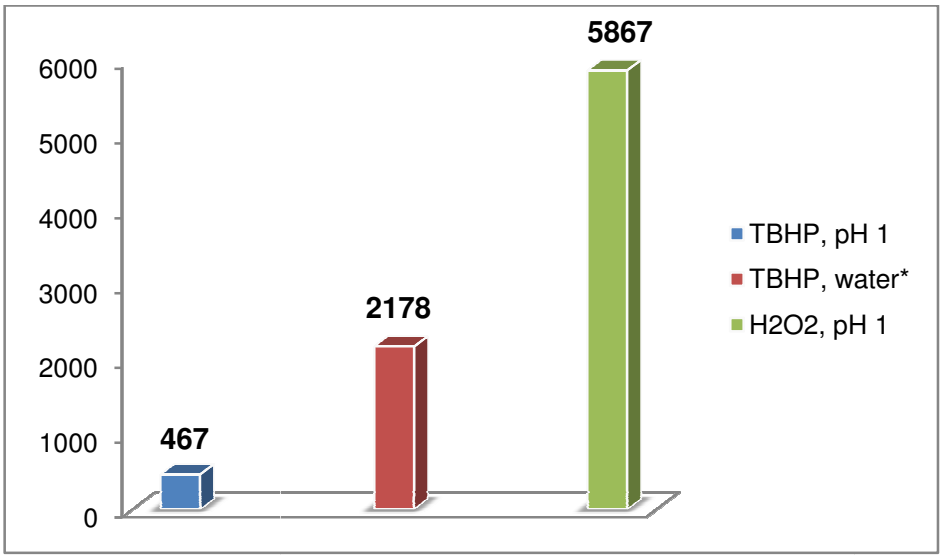


Fig. 9) Turnover frequency comparation.
*** = substrate: 2.6 mmol, cat: 1.5 mol-%, TBHP: 6.5 mmol, reaction time: 3 h at 80° C**

As an attempt to isolate the precatalyst complex, a solution of $FeCl_3$ and 2eq of THA were stirred in MeOH at room temperature for 1h and left slowly evaporate. The residue was investigated by MS-ESI (M^+/q) in the same solvent. The spectrum exhibits a signal at (423) corresponding to $[Fe(THA)_2]^+$ complex and at (731) correlated to a possible dinuclear aggregate (Appendix, Fig 8).

The proposed formulation (A, Fig.8) exhibits the presence of hemilabile carbonyl groups in the aromatic ring and carboxyl moieties, which are responsible to stabilize the Fe(III) cationic complex. In absence of ketone coordination, the resulting cationic tetrahedral complex may include the chloride in the coordination sphere to form a neutral compound or water in the case of the solvated complex. At pH = 1 the protonation of the acetate is likely causing the transformation to mono-hapto coordination. Afterwards the formation of HO-Fe^V =O species trough a water or non-water assisted pathway may be still able to coordinate in cis position, allowing the vicinal coordination of both substrate and oxidant species. A similar coordinative sphere has been observed in the Rieske oxygenase, where the coordination by aspartic acid / histidine is able to stabilize Fe^V metal centre[30] (Fig. 9).

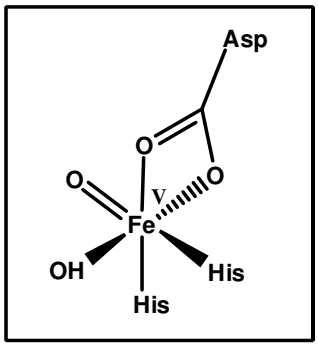


Fig. 10) Rieske's oxigenase, iron center

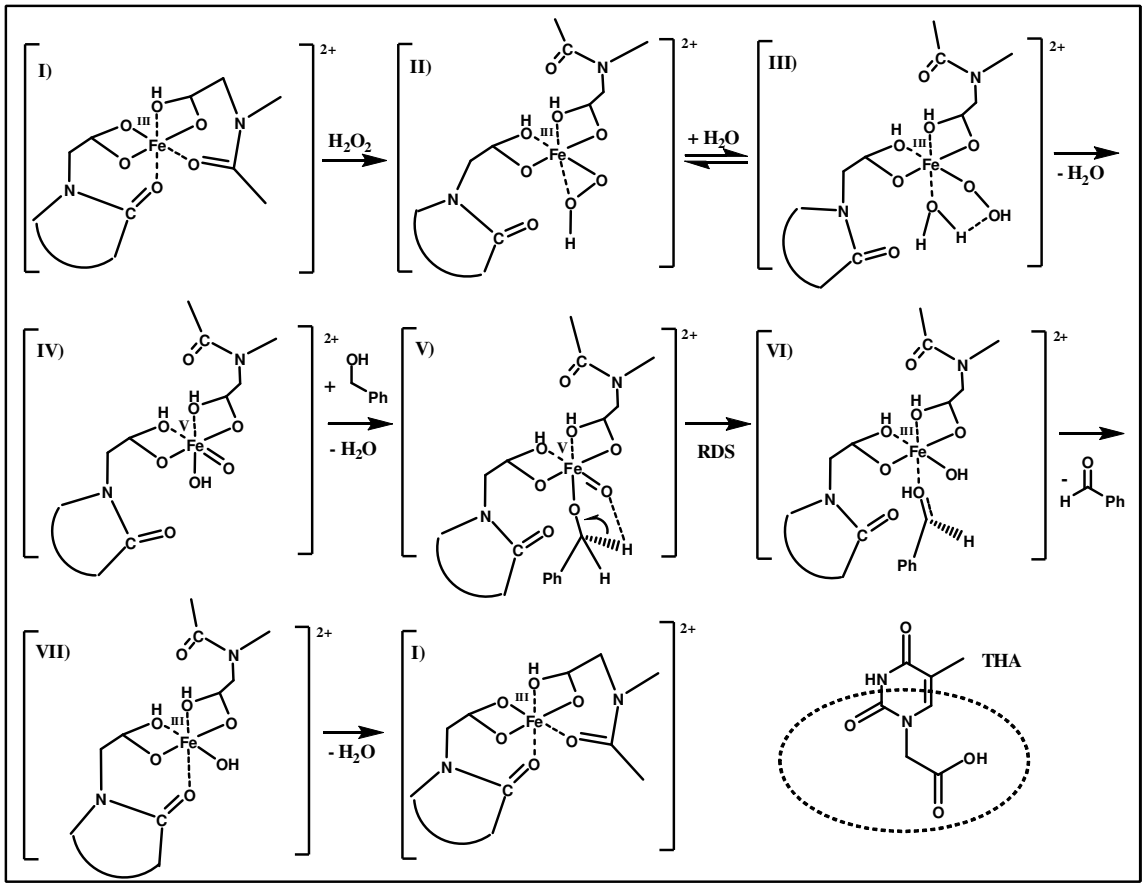


Fig. 11) Proposed mechanism for Fe-THA catalyzed alcohols oxidation, based on literature

A speculative graphic scheme (Fig. 13) based on a presumable mechanism of the oxidative reaction inspired the preliminary DFT calculations sketched in Fig.14. Every complex has been obtained through ab initio calculations, by approaching towards the Fe(III) metal site two equivalent of THA molecules as ligands in a diluted environment of acidic aqueous media (HCl 0.1 M). Therefore, it has been supposed each THA-carboxyl acid would coordinate as carboxylate. The spontaneous rearrangement of the reactants in the vacuum, disposed around the Fe atom, upon the calculation gives rise to the structure **A** designated at 0 kcal mol^{-1}. Both the formally monohapto (k_1)- or chelate (k_2)-THA^- coordinative mode have been exemplified in the starting dication (**A**) in which a proton of THA interacts with the interring C=O function, thus reducing the delocalization of the aromatic representation. The advent of hydrogen peroxide does not influence the stereo-electronic description (**B**) and its energy. The THA is a quite versatile ligand, presenting a moderate sterically demanding six-membered aromatic heteroatomic ring . The ring carbonyls with the ancillary carboxyl pendants act as proton transfer moieties. The coordinated peroxide anion is generated by incorporation of the

proton to the carboxy function (**C**). In the scheme a peroxometalcyclopropane coordination is proposed (Fig. 13). The two THA species nearby the iron atom act therefore as monohapto neutral ligands. The following step (**D**) is concerning the oxidation to the Iron(V)-oxo fragment by releasing a water molecule, which is formed by proton donation from the carboxy function, which is now able to dihapto iron-coordination . Steps C-D requires a moderate amount of energy (about 20 $kcalmol^{-1}$), which is easily recovered in the next steps. The following stadium concerns the access of the benzyl alcohol molecule (**E**). The Fe=O group is then protonated by alcohol, which is coordinated as alcoholate by Fe(V), so the complex results to be globally a dicationic species (**F**). The further interaction implies a $C_{sp3}H$ activation of the benzyl group by proton transfer to a stronger Lewis acid group [Fe^{V}-OH or Fe^{V}=O]. It is noteworthy noting that this is supposed to be the rate determining step of the reaction.

Ultimately, both the carboxyl protons might migrate to Fe=O(V) in the reductive elimination. So, the resulting complex can finally releases benzaldehyde and water, with an overall energy gain of about of 57 kcal mol^{-1} , reconstructing the initial complex (**A**). The calculations are not comprehensively exhaustive and not finished yet. This path is one of the possible sketchable mechanisms, which propose a model for a biomimetic oxidative reaction, however it is an attempt to rationalize and elucidate on an hot issue. Both the first draft hypothesis and the DFT-calculated results lead to a very similar mechanistic path, confirming our preliminary speculations. The calculated global energy gain of the benzyl alcohol oxidation by hydrogen peroxide (ΔH energy balance) results congruent to that one based on the relative enthalpies of the benzaldehyde and water formation in the gaseous phase and normal conditions (Fig. 12).

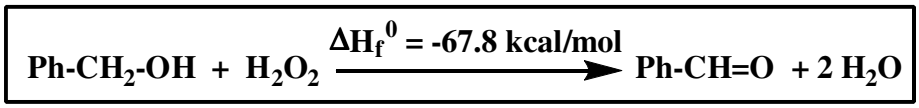
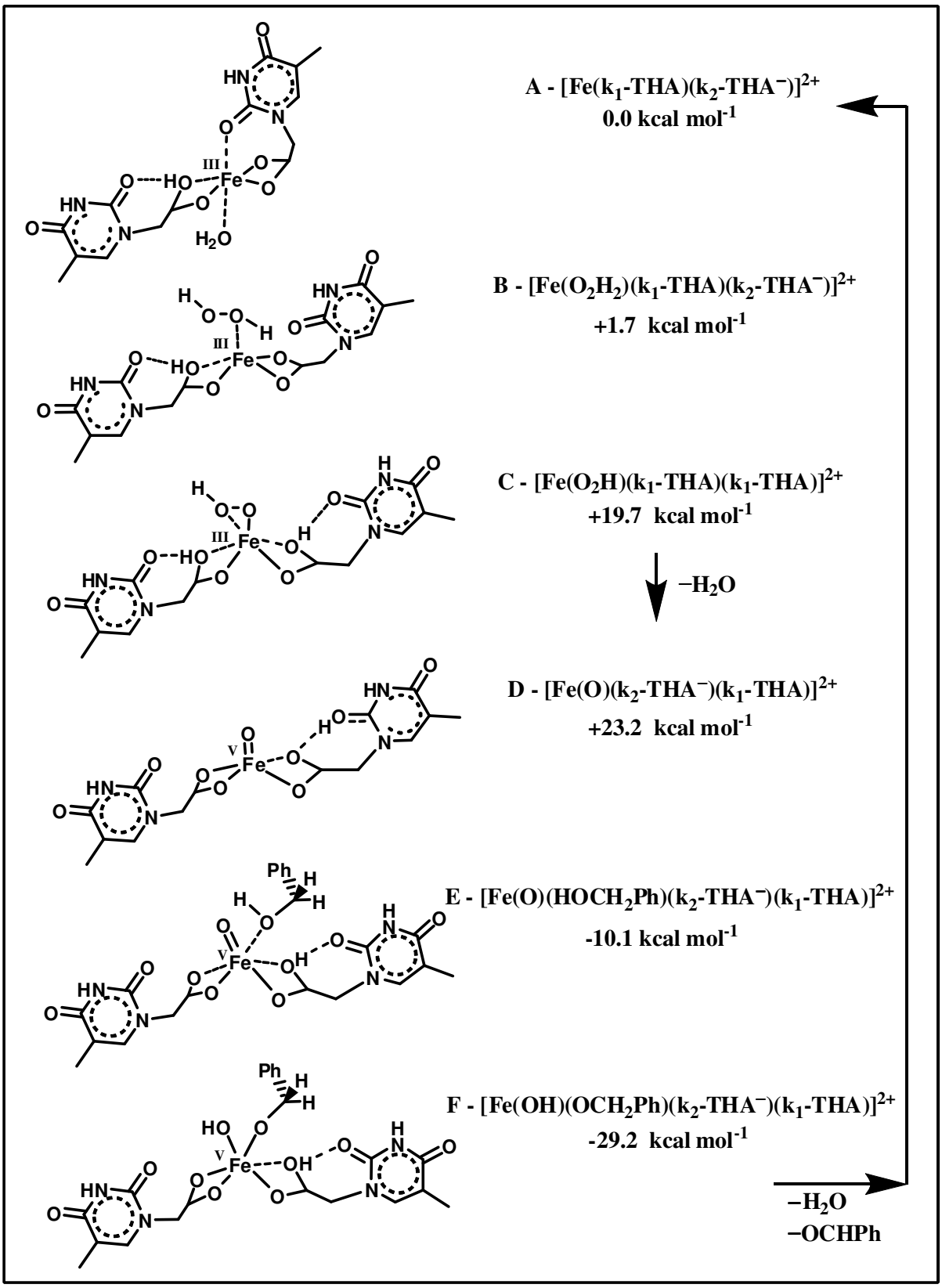


Fig.12) Reaction energy based on formation enthalpy values[31]

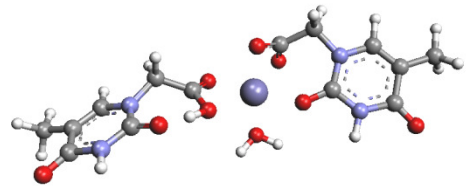


Scheme 13) Speculative scheme on a presumable oxidative reaction path for benzyl alcohol
THA = [Thymine-CH_2-COOH]
THA = [Thymine-CH_2-COO^-]

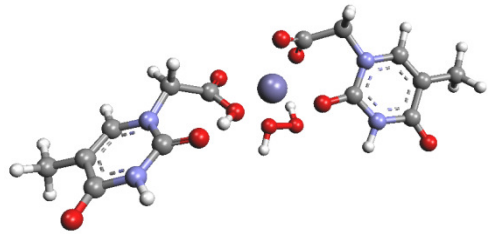
Ab initio calculation

starting molecules:

- **Fe**
- **2 THA**
- **Benzyl alcohol**
- **H_2O_2**
- **H_2O**
- **H^+**



A



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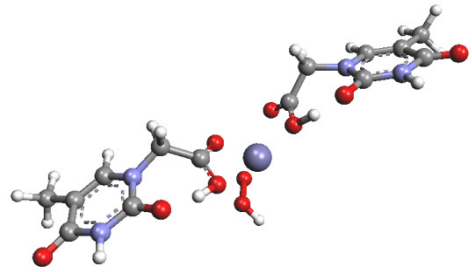
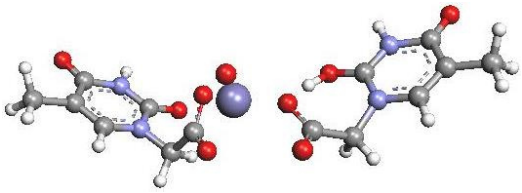
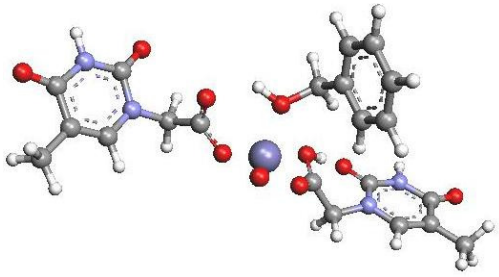


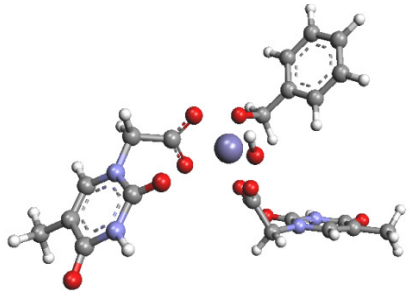
C



D



E



F

Scheme 14) DFT calculations and corresponding structures of a presumable oxidative reaction path for benzyl alcohol

3) C-H Activation

The carbon-hydrogen bond is for definition the *un-functional* group. This fact is well reflected by the general "invisibility" of these bonds in the common organic chemistry representation. Since the C-H bond is the most abundant chemical bond in nature, developing a route to selectively functionalize it, may constitute the most powerful and broadly applicable chemical transformation[32]. A deep understanding of C-H bonds properties such as accessibility and reactivity is fundamental to ensure the selectivity between the large numbers of possible active sites[33]. Many transition metals have been proved to play key roles in highly efficient C-H activation such as Pd[34], Ir[35], Rh[36], Pt[37] and Ru[38], but the high price and the considerable toxicity limit their applications and future improvements. The importance of developing valid iron catalyzed C-H transformations, which combine both advantages derived from iron chemistry (atoxic, unexpensive, disposable) and C-H activation, fully justified the rapid increase of publications in the last decade[39].

3.1) Oxidative C-H activation and Iron role

The target of the oxidative C-H activation is the insertion of oxygenated functional group in an un-reactive C-H bond. The direct activation of these bonds has the advantage of keep them inert until the selective oxidation occurs, but there are questions concerning how to realize the process and how to guarantee useful levels of selectivity in organic macro-molecules. Barton[40] defined *Gif* oxidations (from the Gif-sur-Yvette Institut de Chimie), reactions which present the ability to functionalize saturated molecules to ketones by non-radical pathways, discussing the reasons why a radical pathway cannot provide selective transformation.

The ability to perform efficient and region-selective direct hydroxylation or alkene epoxydation, has been restricted to the enzymes realm for many years, especially to Cytochrome P450 family. Non-heme iron enzymes such as methane monoxygenase[41] and Rieske dioxygenase[42] successfully catalyze alkane C-H oxidations, inspiring researches in this field in order of developing new catalyst models (Fig. 5). The conversion of an alkyl C-H bond into C-O is a thermodynamic highly favorable transformation, but strong oxidizing agents are needed to overcome the kinetic inert nature of C-H bonds, raising other challenges to ensure the selectivity[43].

As a key step, it has been proposed that the catalyst iron centre forms an highly oxidizing oxo-iron species. In P450 family, the active species is best described as an oxo-Fe(IV)-porphyrin radical cation, which is stabilized by the redox non-innocent ligand ring. On the other hand, the Rieske dioxygenase family is formally represented by a non-heme group and the reactive core is postulated as an oxo-Fe(V) species. In 1997, Que Jr. reported the first example of a non-heme iron catalyst working with H_2O_2 capable of stereospecific alkane hydroxylation.[44] Further studies[45] clearly indicate the importance of substituent groups on multidentate nitrogen ligands, which modify electronic and steric properties, thus can significantly improve reactivity and selectivity of the catalyst.

In line with this approach, in 2007 White and co-workers provided a considerable contribution. They reported[46] C-H activation on primary, secondary and tertiary C-H bonds, studying the combined influence of electronic and steric effects, with the purpose to find a general protocol for oxidative C-H activation. Their most important finding is related to the electronic primary role in the C-H bond breaking, so that tertiary alcohols reacts faster than primary ones(Fig. 1). They find that an electron-withdrawing group in α or β position decrease the electron density of the vicinal C-H, making it less reactive and thus inducing selectivity towards the remote C-H group. They investigated the most challenging methylene activation in more elaborated substrates, the reactivity prediction based on combined electronic and steric effects was proved. The goal of this approach is to provide new strategies for selective C-H oxidation in challenging substrates.[47]

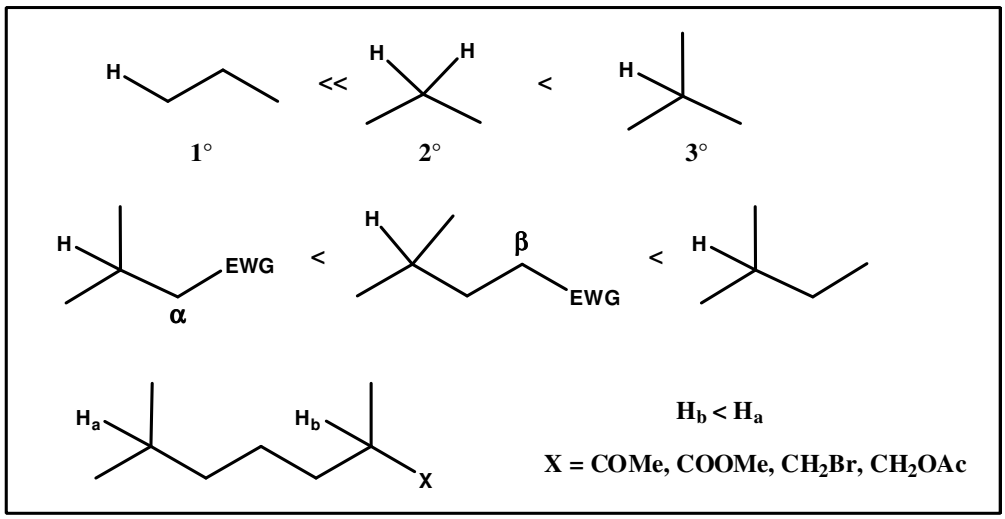


Fig. 1) Reactivity of different C-H bond

Costas modified White's catalyst and the Que's triazacyclononane ligand, founding the TACN ligands family, realizing in both cases successful examples of C-H activation.[48] He also investigated the reaction mechanism findings in accordance with Que's studies.

Examples of enantio-selective C-H activation were successfully reported by Que[49] involving bio-inspired iron complexes bearing chiral ligands.

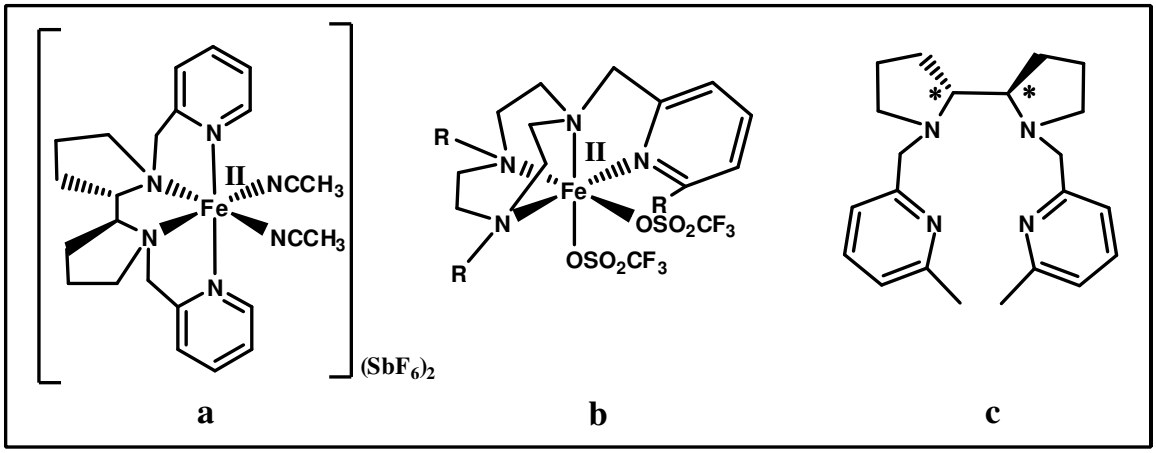


Fig. 2) a) White's catalyst, b) Costas's catalyst, c) Que's chiral ligand

A key role of Fe(III)-OOH hydroperoxo species has been proposed[50] but after disproved by EPR spectroscopy studies[51] and later by oxygen labelled investigations.[52] The formation of the Fe(III)-OOH species was not influenced by the presence of substrate, proving that the direct oxidation is not possible[49]. Incorporation of ^{18}O in the substrate by isotopically labelled water was studied. As a result, iron (III) peroxo species was not able to perform ^{18}O exchange with water, thus excluding it to have a key role in this transformation. A common reaction mechanism for alkane hydroxylations and alkene epoxidations with non-heme iron catalyst has been proposed by Costas and Que. Their results, based on the ^{18}O labelling experiments, strongly suggest the HO-Fe^{V}=O as the key oxidant.[53]

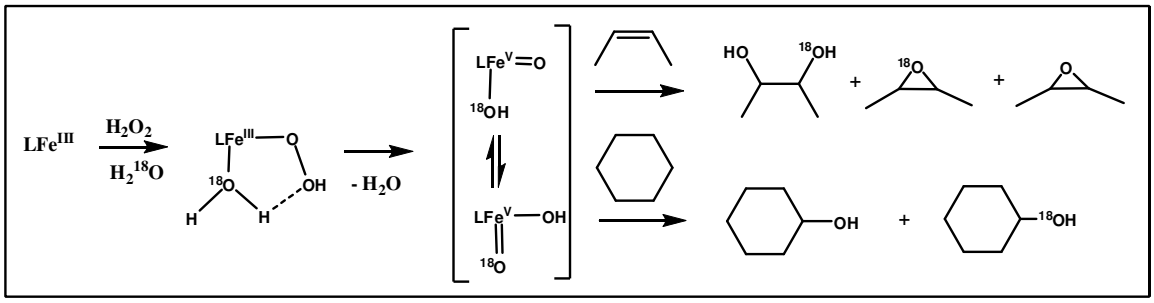


Fig. 3) Proposed mechanism for water assisted oxidation[54]

For many years Fe^{V} was designed to have a key only in theory, since only one[55] synthetic oxo-iron^{V} has been stable enough to be spectroscopically characterized and on the other hand, it was not able to realize C-H cleavage or C=C oxidation.

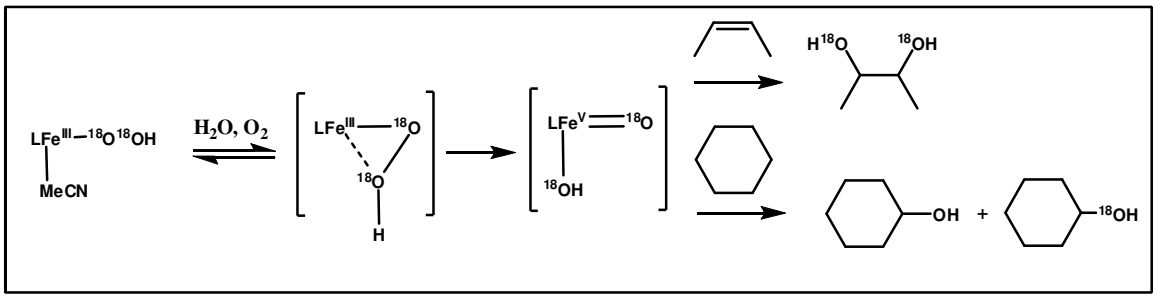


Fig. 4) Proposed mechanism for non-water assisted oxidation [56]

In 2011 Que reported the observation of transient Fe^{V} intermediates via variable-temperature mass spectroscopy during alkane oxidation. The reaction was catalyzed by a non-heme iron complex[57] and H_2O_2 as oxidant (Fig. 5). The mass spectrum revealed a peak corresponding to Fe^{V} species only below -10 °C and the signal intensity was found to increase at lower temperatures. This suggests the occurrence of a transient species involved in the catalytic cycle. Isotopic labelling with ^{18}O confirms the prevision, each oxygen atom in the hydro-oxo-iron can be attributed, one comes from the oxidant H_2O_2 and the other one derives from the solvent H_2O. However, the extension of these proposed reaction schemes to other iron non-heme systems has to be carefully evaluated.

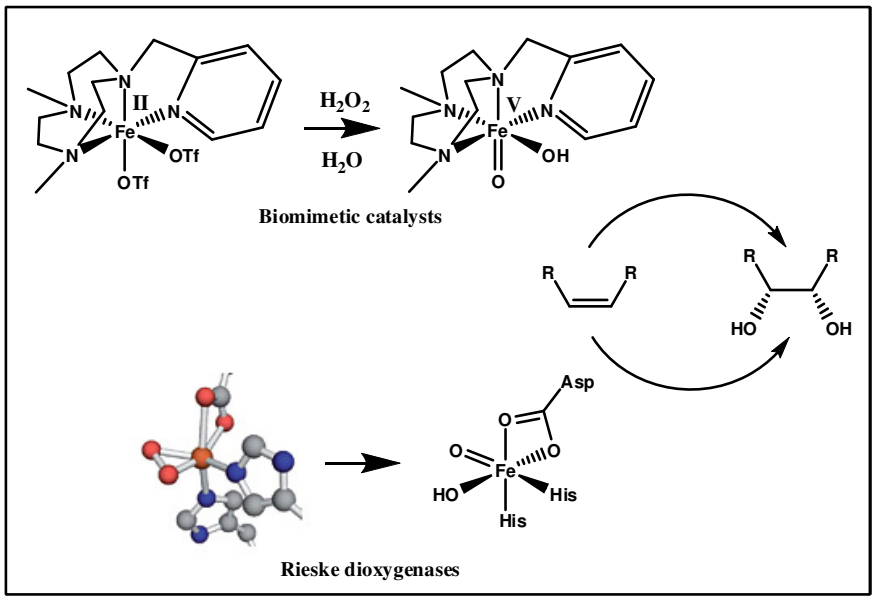


Fig. 5) Alkene cis-dihydroxylation mediated by (hydroxo)oxoiron(v) species[56]

A further purpose of this work is to study the catalytic Fe-THA system in the most challenging topic of C-H activation. The later includes simple halogen sources such as ammonium salts combined with H_2O_2 in mild reaction conditions to obtain direct oxygen and halogen insertion in one-pot reactions.

3.2) Oxygen functionalization

Direct oxygen insertion into molecules like cyclohexane and cyclohexene under mild conditions is an industrial issue of great relevance[58]. These compounds represent valid starting materials for adipic acid or intermediates[59], thus a large number of scientific publications is disposable about this topic. Adipic acid is an important bicarboxylic acid used mainly as a starting material for the production of nylon-6,6, a polymeric material of everyday use, including clothing and carpet fibers, tyre reinforcement, automobile, etc. Current industrial processes[60] use a mixture of cyclohexanol and cyclohexanone as starting material, derived from petroleum fractions via optimized high temperature processes. This mixture commonly called Ketone-Alcohol-oil (KAoil) is transformed to adipic acid with an oxidative process involving stoichiometric use of nitric acid with emission of nitrous oxide (Fig. 6) The release of 0.3 tons of N_2O per ton of adipic acid produced, contributes to global warming and ozone depletion[61]. Succinic and glutaric acids are usually obtained as by-products. The use of nitric acid is still preferred because of the cheap price, despite the corrosive power affect the plant's costs and cause gaseous and liquids effluents treatment.

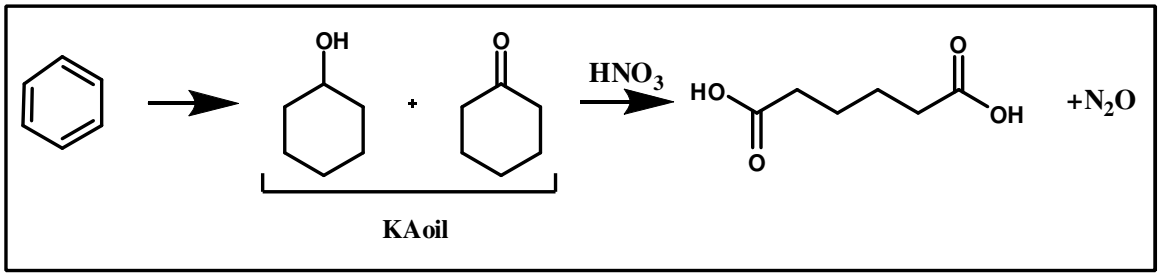


Fig. 6) Industrial production of adipic acid

The development of more environmental benign processes is of crucial importance[62]. The most promising and greener method to synthetize adipic acid implies oxidation of cyclohexene with hydrogen peroxide. In 1998 Sato and Noyori[63] proposed an effective method to convert cyclohexene to adipic acid through a multistep oxidation process, catalyzed by sodium tungstate with H_2O_2 as primary oxidant. First step involves epoxide formation followed by hydrolysis to afford a diol species. Then a Bayer-Villiger oxidation occurs and multiple hydrolysis steps lead to diacid. This system presents good performance but the industrialization has not been realized because of technical problems concerning products purity and catalyst recyclability in scaled-up reactors.

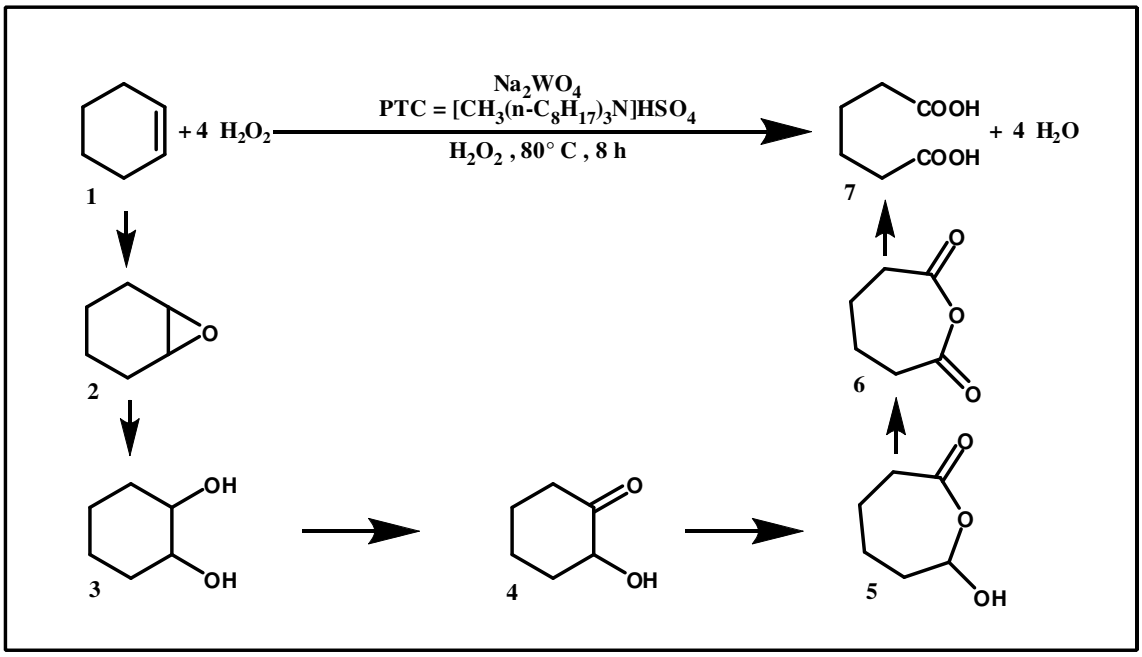


Fig. 7) Generally accepted reaction pathway for the direct oxidation of cyclohexene proposed by Noyori

Another approach in the field is represented by the biomimetic catalysis, involving for example iron porphyrins for realizing direct oxidation of cyclohexane to adipic acid[64].

In order to develop new routes for direct functionalization of unreactive C-H bonds, various reaction configurations were tested involving the in-situ generated Fe-THA catalyst and H_2O_2 as primary oxidant used in alcohol oxidations. We tried to adapt the green Fe-THA catalytic system to realize direct oxygen insertion in saturated molecule such as cyclohexane and cyclooctane. We also tried to reproduce the oxidative transformation of cyclohexene to adipic acid as proposed by Noyori and Sato[65]. Since substrates and products might be volatile, the adoption of sealed glass micro-reactor equipped with metal-silicon caps was needed to avoid any gaseous losses.

3.3) Halogens insertion

Insertion of halogen groups into un-reactive molecules is an important issue for chemical industry. Halogenated organic compounds are important synthetic intermediates, due to their feasible transformation into a variety of functional molecules[66], mainly via nucleophilic attack. Halogen-based oxidants such as elemental halogens, organic and inorganic hypohalites, hypervalent iodine (III) and (V), dihalo-5,5'-dimethylhydantoins are often used for selective halogenations of unsaturated hydrocarbons[67]. The resulting products, vicinal halohydrins and dihalides, are versatile intermediates for the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals, additives, plasticizers and specialities[68]. However, most of the mentioned reagents are toxic, expensive and produce stoichiometric amount of waste. N-halosuccinimides (NHS) have been widely studied as a mild halogens source and because of their unique chemical and physical properties together with the easy handling[69]. The high polarity helps in dissolution of both organic and inorganic species increasing the reaction rate. This aspect is of particular interest for the pharmaceutical industry, where organic salts represents 50% of the production. N-halosuccinimides are generally considered as green recyclable alternatives, but the following issues limit their use: stoichiometric reactant, low atom economy, high toxicity for aquatic environments, non-rare tricky work up and recycling which involve halogens. These factors contribute in rise up production costs and limiting the diffusion of NHSs as halogenations agents.

Based on nature's oxidative halogenations, a greener strategy consists of generating the halogenating reagent in situ from an halide salt under acidic conditions[70]. This approach permits quantitatively halogen insertion, preventing the generation of halogenated waste. In nature the electrophilic halogenation mainly occurs by oxidative halogenation through a catalytic oxidation of the halide ion to form an halogenating reagent. Based on biomimetic studies[71], a plausible mechanism for olefin halogenations is show in Fig. 8 , where the in-situ generated halonium cation performs the electrophilic attack on a C=C double bond. The subsequent attack by HO^-, Br^-, RO^- ions for example, provide the corresponding halohydrins, dihalo-compounds and halo-derivatives. Further oxidation step may result in an α-haloketone species.

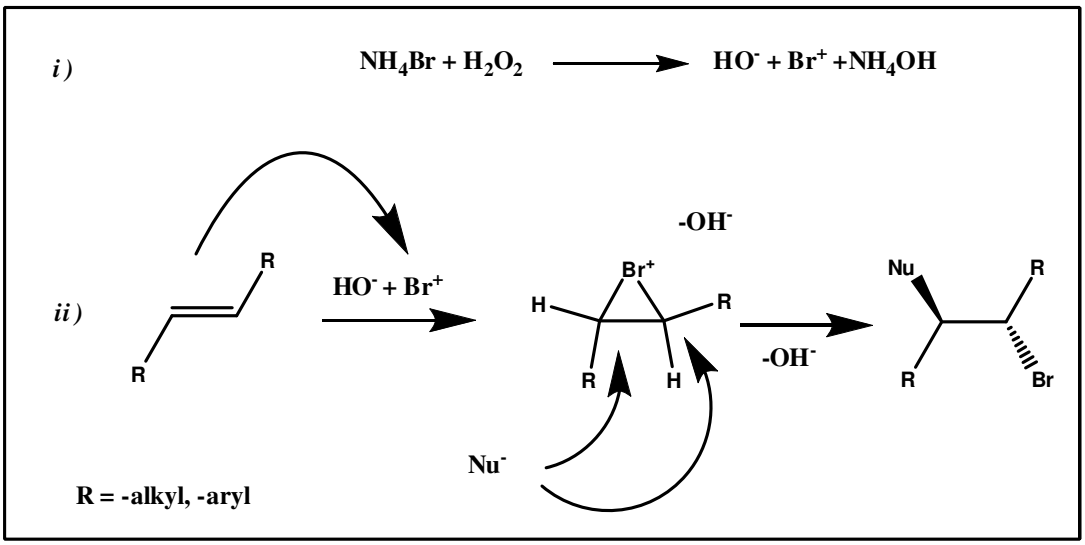


Fig. 8) Possible olefins bromination pathways[72]

We suppose that the Fe-THA complex is able to perform an oxidative catalytic cycle for olefins functionalization similarly to what proposed for bromonium active species. Important reaction differences have been observed along the halogens group, bromonium was isolated many years ago,[73] while chloronium ion has never been observed. Therefore it is probable that the reaction pathway in Fig. 8 is not valid for chlorine, while the proposed mechanism implies the C=C catalytic oxidation of olefin to epoxide, which subsequently undergoes a nucleophilic attack by the halide. The direct oxidative transformation of olefins to α-halohydrins or α-haloketones provides 1,2-difunctionalized synthons, useful starting material for building heterocyclic rings such as imidazoles,[74] oxazoles,[75] thiazoles,[76] triazoles,[77] benzofurans,[78] 1,4-benzodioxans,[79] pyrazines[80] and others[81].

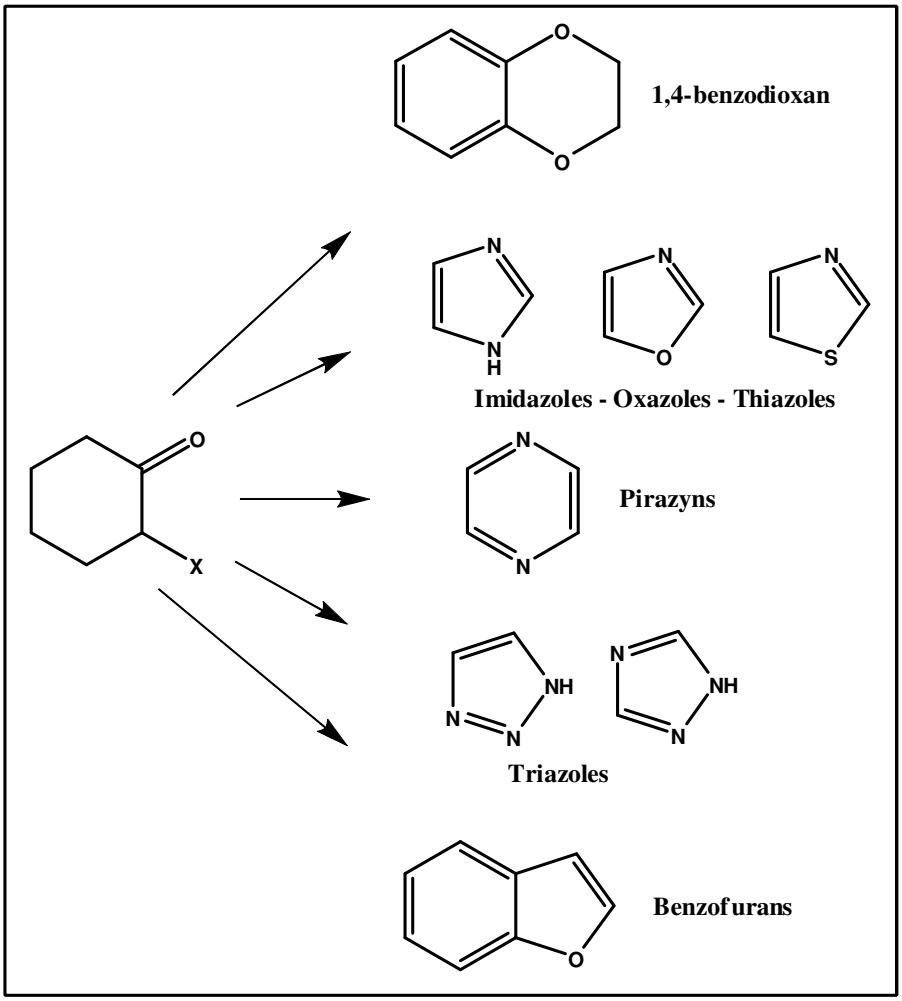


Fig. 9) α-Halohydrins and α-Haloketones as useful synthons

In literature, the majority of α-haloketones are prepared by halogenation of the corresponding ketone, instead only limited synthetic protocols are available concerning olefin transformation.[82]

Different halogen sources have been introduced in the Fe-THA catalyzed oxidative transformation of olefins to obtaining corresponding bromo and chloro derivatives of synthetic interest.

4) Experimental part

General informations

All compounds, solvents and metal salts were purchased from Sigma Aldrich and used as received. Buffer solution was AVS TITRINORM® pH=1 (20° C), constituent Glycin, NaCl, HCl in water. Hydrogen peroxide was purchased from VWR BDH Prolabo (33 $\%_{m/v}$ aqueous solution).

The pumping system is composed a syringe pump equipped with a plastic 1 mL syringe and PFTE 1/16 inch tube to the reactor. Reaction products were identified quantitatively by GC (Agilent 6890 chromatograph, Agilent 19091 J-413 capillary column 0.32 mm-30 m-0.25 µm, FID detector) using decane as an internal standard.

Products were identified by GC-MS analyses (Agilent 6890N equipped with Agilent 5973 mass selective detector, DB-innowax 19091 L-102 capillary columns, 0.20µm-24 m-0.31 mm) and/or by NMR spectra were measured on a Varian Gemini spectrometer 300 MHz (^{1}H).

All density functional computations have been performed using the Molpro2010 suite of quantum chemistry programs.[83] The chosen density functional was the Perdew–Burke–Ernzerhof hybrid exchange-correlation functional (also called PBE0)[84] in conjunction to the compact SVP basis set of Ahlrichs et al.[85] All geometry optimizations of the reaction intermediates have been performed in cartesian coordinates, starting from approximate guess geometries devised by means of the freely available Arguslab program. [86]

GC sample preparation

Reaction mixtures were quenched with Na_2SO_3 and cooled in an ice bath. In solvent-free reactions condition, a sample was taken, filtered through a silica layer in a Pasteur pipette and then injected in a GC-FID. Alternatively for GC-MS analysis, the sample (1 mL) was extracted with EtOAc (3 X 1 mL) in an extraction funnel, dried with $MgSO_4$ and filtered through a silica layer in a Pasteur pipette. For reactions in organic solvent, a sample was taken, dried with $MgSO_4$, filtered through a silica layer in a Pasteur pipette and injected into GC-MS.

4.1) Alcohol Oxidations

4.1.1) [Fe(1,10-phenantroline)$_2$Cl$_2$] NO$_3$ Complex

Preparation procedure of complex [Fe(phen)$_2$Cl$_2$]NO$_3$ (1) [26]:

A solution of 1,10-phenantroline (4 mmol, 0.720 g) in acetic acid : water (6:4 , 5mL) was added drop-wise to a solution of $FeCl_3 \cdot 6\ H_2O$ (1 mmol, 0.270 g) in the same solvent (10 mL) while slowly stirring (450 rpm) at RT. After 30 min, solid $[Ce(NO_3)_6](NH_4)_2$ (1 mmol, 0.550 g) was added portion-wise to the solution, the stirring was continued for other 30 min. The pink solution slowly turned red, the supernatant liquid was kept in air for slow evaporation. After a week, complex (1) was filtered, washed with hexane and dried under vacuum. Yield (based on the metal salt): 80%.

MW : 549.18 g/mol. IR (KBr pellet): ν =1384 (s), 1426 (m), 1517 (s) cm^{-1}.

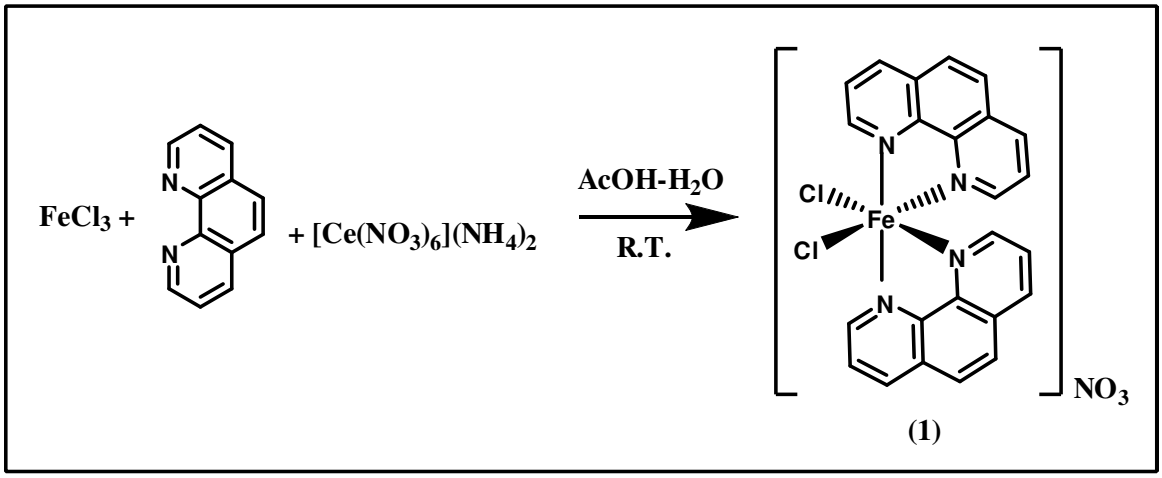


Fig. 1) [Fe(phen)$_2$Cl$_2$]NO$_3$ complex synthesis

General method for alcohol oxidations

In a 25 ml round bottomed flask equipped with rubber caps and magnetic stirring, complex (**1**) (0.015 mmol, 1.5 mol-%) was dissolved in the buffer solution (3 mL, HCl/Gly pH=1), afterwards substrate (1 mmol) and internal standard (decane, 200 µL) were added and vigorously stirred at 55°C. The reaction started by adding the first drop of H_2O_2 (2.2 mmol, in 10 min) trough a syringe pump. After a variable time (30-120 min), the reaction was quenched by addition of sodium sulfite (Na_2SO_3), and a sample was subjected to GC analysis.

4.1.2) [Fe(THA)$_2$S$_2$] (S=H$_2$O, Cl$^-$, MeCN) in-situ generated complex

General method for alcohol oxidations

$FeCl_3 \cdot 6\ H_2O$ (0.03 mmol, 3 mol-%) and THA (0.06 mmol, 6 mol-%) were stirred in a buffer solution (3 mL, HCl/Gly pH=1) in a 25 ml round bottomed flask equipped with rubber caps, for 1 h at 55°C. Afterwards the substrate (1 mmol) was added and the reaction was started by adding a drop of oxidant (2.2 mmol in 10 min) by a syringe pump. After a variable time (30-120 min), the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

4.2) Oxidative C-H activation

4.2.1) Oxygen insertion

Cyclooctane oxidation (Entry I)

$FeCl_3 \cdot 6\ H_2O$ (8.1 mg, 3 mol-%) and THA (10.8 mg, 6 mol-%) were stirred in a 10 ml sealed test tube with a buffer solution (3 mL, HCl/Gly pH=1) and 0.5 mL of Bu_4NHCO_3 solution (0.18 M in MeCN) for 1h at 55°C. Afterwards cyclooctane (1 mmol, 135 µL) was added and the reaction was started by adding a drop of oxidant (3 mmol in 15 min) by a syringe pump. After 8 h the reaction was quenched by the addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Cyclohexane oxidation (Entry II)

$FeCl_3 \cdot 6\ H_2O$ (8.1 mg, 3 mol-%) and THA (10.8 mg, 6 mol-%) were stirred in a 10 ml sealed test tube with a buffer solution (3 mL, HCl/Gly pH=1) and 0.5 mL of Bu_4NHCO_3 solution (0.18 M in MeCN) for 1h at 55°C. Afterwards cyclohexane (1 mmol, 60 µL) was added and the reaction was started by adding a drop of oxidant (3 mmol in 15 min) by a syringe pump. After 8 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Cyclohexane oxidation (Entry III)

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with MeCN (3 mL) and 0.2 mL of Bu_4NHCO_3 solution (0.18 M in

MeCN) for 1h at 55°C. Afterwards cyclohexane (1 mmol, 60 µL) was added and the reaction was started by adding a drop of oxidant (3 mmol in 15 min) by a syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Cyclohexene oxidation experiments

HCl solution (Entry 1):

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a buffer solution (3 mL, HCl/Gly pH=1) and 0.5 mL of Bu_4NHCO_3 solution (0.18 M in MeCN) for 1h at 55°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (4.4 mmol in 15 min) by a syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

H_3PO_4 solution (Entry 2):

$Fe(Ac)_3$ (11.7mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a buffer solution (3 mL, H_3PO_4/ NaH_2PO_4 pH=1) and 0.5 mL of Bu_4NHCO_3 solution (0.18 M in MeCN) for 1h at 55°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (4.4 mmol in 15 min) by syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

MeCN solution (Entry 3):

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with MeCN (3 mL) for 1h at 55°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (4.4 mmol in 15 min) by a syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

4.3) Halogens insertion

Olefins Chloro-hydroxylation

Entry 1

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with MeCN (3 mL) and Bu_4NCl (1.2 mmol, 292 mg) for 1h at 60°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (2 mmol in 15 min) by a syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 2

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a MeCN/CH_3COOH solution 2/1(3 mL) and Bu_4NCl (1.2 mmol, 292 mg) for 1h at 60°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (1 mmol in 15 min) by a syringe pump. A new oxidant amount (1 mmol) was added after 3 h. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 3

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a HCl buffer pH=1 /CH_2Cl_2 mixture 1/1 (3 mL) and Bu_4NCl (1.2 mmol, 292 mg) for 1h at 30°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (1 mmol in 15 min) by a syringe pump. A new oxidant amount (1 mmol) was added after 3 h. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 4

$FeCl_3 \cdot 6\ H_2O$ (13.5 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with MeOH (6 mL) and NH_4Cl (1.2 mmol, 64.2 mg) for 1h at 60°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by

adding a drop of oxidant (2 mmol in 15 min) by a syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Olefins Bromohydroxylation

Entry 5

$Fe(NO_3)_3 \cdot 9\ H_2O$ (20.2 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a MeCN/CH_3COOH solution 2/1 (3 mL) and Bu_4NBr (1.2 mmol, 387 mg) for 1h at 60°C. Afterwards cyclohexene (1 mmol, 100 µL) was added and the reaction was started by adding a drop of oxidant (1 mmol in 15 min) by a syringe pump. A new oxidant amount (1 mmol) was added after 3 h. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 6

$Fe(NO_3)_3 \cdot 9\ H_2O$ (20.2 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with a MeCN/CH_3COOH solution 2/1 (3 mL) for 1h at RT.
NH_4Br (1,2 mmol, 118 mg) is dissolved apart in H_2O_2 (33% $_{m/v}$ in water, 4.4 mmol)
Afterwards cyclohexene (1 mmol, 100 µL) was added in the vial, the reaction started by adding a drop of halogen salt-oxidant mixture. The total oxidant volume was introduced in 5 min by a syringe pump. After 30 min the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 7

$Fe(NO_3)_3 \cdot 9\ H_2O$ (20.2 mg, 5 mol-%) and THA (18 mg, 10 mol-%) were stirred in a 10 ml sealed test tube with MeOH (6 mL) for 1h at RT.
NH_4Br (1,2 mmol, 118 mg) is dissolved apart in H_2O_2 (33% $_{m/v}$ in water, 4.4 mmol)
Afterwards cyclohexene (1 mmol, 100 µL) was added in the vial, the reaction started by adding a drop of halogen salt-oxidant mixture. The total oxidant volume was introduced in 5 min by a syringe pump. After 30 min the reaction was quenched by the addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Entry 8

$Fe(NO_3)_3 \cdot 9\ H_2O$ (28.3 mg, 7 mol-%) and THA (25,2 mg, 14 mol-%) were stirred in a 10 ml sealed test tube with MeOH (6 mL) for 1h at 60 °C.

NH_4Br (1,6 mmol, 157 mg) is dissolved apart in H_2O_2 (33% $_{m/v}$ in water, 16 mmol)

Afterwards cyclohexene (1 mmol, 100 µL) was added in the vial, the reaction started by adding a drop of halogen salt-oxidant mixture. The total oxidant volume was introduced in 30 min by a syringe pump. After 60 min the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

Fluorination

A $Fe(SO_3CF_3)_3$ and THA solution in phosphate buffer pH=1 was prepared, with 1:2 ratio. $Fe(Ac)_3$ (1 mmol, 70.2 mg) and HSO_3CF_3 (4.5 mmol) have been mixed in MeCN (3 mL) for 1 h at RT before been dried and newly dissolved in the phosphate buffer solution.

A solution volume corresponding to 5 mol-% of $Fe(SO_3CF_3)_3$ is mixed with THA (10 mol-%) and stirred in a 10 ml sealed test tube for 1h at 55 °C. Afterwards cyclohexene (1 mmol, 100 µL) and Bu_4NF (1,3 mmol, 410 mg) were added, , the reaction started by adding a drop of oxidant (2 mmol in 15 min) by syringe pump. After 20 h the reaction was quenched by addition of sodium sulfite (Na_2SO_3) and a sample was subjected to GC analysis.

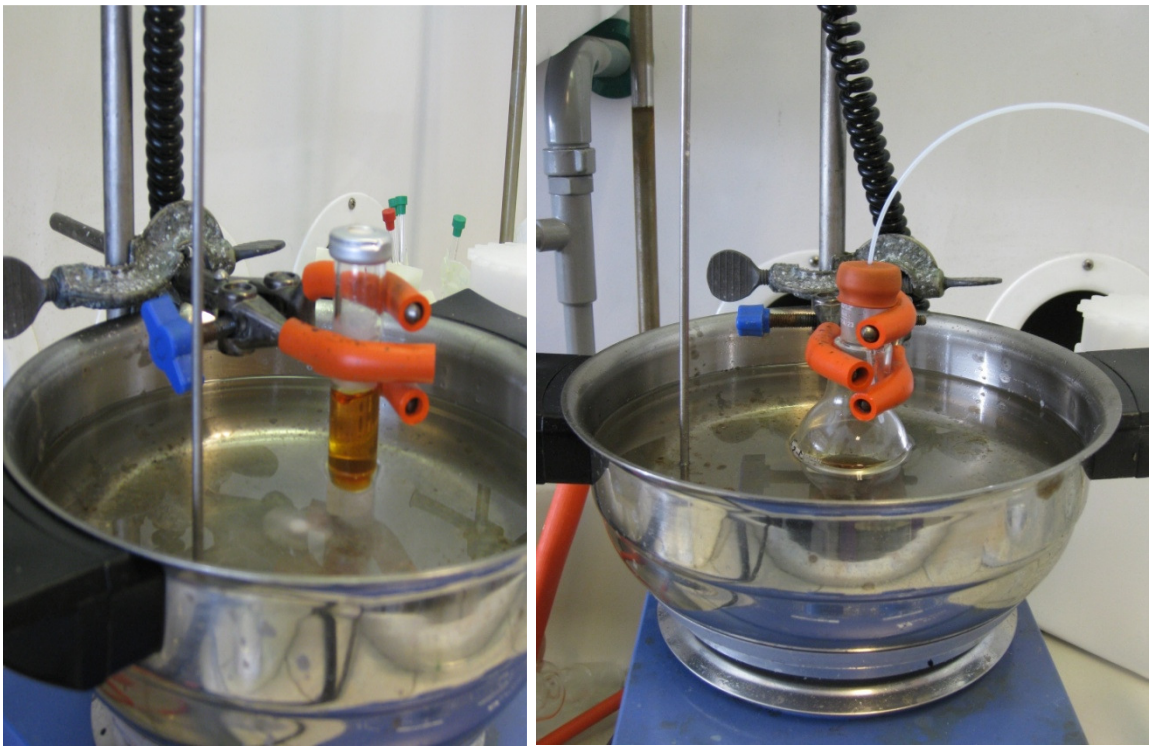


Fig. 2) Standard reaction configuration

Molecular weights

$FeCl_3 \cdot 6\ H_2O$ = 270.30 g/mol

$Fe(NO_3)_3 \cdot 9\ H_2O$ = 404.02 g/mol

THA = 184.15 g/mol

1,10-Phenantroline = 180.21

Bu_4NBr = 322.4 g/mol

Bu_4NCl = 277. 92 g/mol

Bu_4NF = 315.51 g/mol

NH_4Br = 97.95 g/mol

NH_4Cl = 53.49 g/mol

ACN = 548.26 g/mol

Benzyl alcohol = 108.14 d = 1.049 g/ml

Cyclohexene = 82.14 g/mol d = 0.811 g/ml

5) Result and discussion

5.1) Alcohol oxidations

See alcohol oxidations discussion above, Chapter 2.

5.2) Oxidative C-H activation

Cyclooctane (**Entry I**) was chosen as a substrate since the presence of a ring strain make it easier to oxidize than those with six-membered ring structures. The oxidation was realized in aqueous buffer pH 1 with a small amount of Bu_4NHCO_3 in MeCN to enhance the miscibility between organic substrate and aqueous environment. The reaction affords the 86% of conversion to cycloctanone (54%) and 1,4-cyclooctanedione (46%) in 8 h at 55° C with 3 mol-% of Fe-THA catalyst. Cyclohexane (**Entry II**) was oxidized in the same reaction conditions but with very low conversion to cyclohexanone. The observed lack of selectivity may be ascribed to the low miscibility in water and highest stability of the six-member ring. It is noteworthy that the least reactive substrate (cyclohexane) undergoes a competitive halogenations because of the drastic acidic conditions adopted. Cyclohexane oxidation was realized even in acetonitrile (**Entry III**), by using higher catalyst amount and 20 hours reaction time. The conversion was of 52% mainly to cyclohexanone (62 %). Other products are undesired chloro-substitued molecules.

Entry	I	II	III
Conversion [%]	86	5	52
Cyclooctanone	54	x	x
1,4-Cyclooctanedione	46	x	x
Cyclohexanone	x	88	62
Chloro-cyclohexane	x	12	20
3-Hydroxy-Cyclohexanone	x	0	4

Table 1) Oxidative C-H activation GC-MS % results

Cyclohexene

Although different environmental conditions were tested, the substrate conversion was unsatisfactory in most of the cases. In **Entry 1,** a quaternary ammonium salt was added as a phase transfer agent, in order to increase the contact surface between the aqueous catalyst and the organic phase. It was observed that under these conditions, the chloride anion competes with water for the epoxide-ring opening via nucleophilic attack, giving halohydrin as main products. 1,2-Dichlorocyclohexane is generated in the same way by nucleophilic attack on the C-OH bond. For each Entry, products generated by direct C-H activation were observed, Table 2, [2]-[3].

In a halogen-free environment, **Entry 2,** it is possible to get a selective ring opening of epoxide by water to diol compounds, but some considerable amount of direct oxidation products are also produced. Introducing MeCN as solvent, **Entry 3,** the nucleophilic force for the ring opening is lost, resulting in the formation of cyclohexane oxide as main product together with cyclohex-2-enone. The higher conversion obtained is probably due to a better contact between reagents.

Entry	1	2	3
Conversion %	5	5	30
cyclohex-2-enol [2]	45		8
cyclohex-2-enone [3]		34	30
Cyclohexane oxide [4]			44
Cyclohexane diol [5]		62	18
2-hydroxy cyclohexanone [6]		4	
2-chloro cyclohexanol [8]	45		
1,2-dichloro cyclohexane [10]	10		

Table 2) : Cyclohexene oxidations GC-MS % results

In Fig. 1 is reported the product distribution observed in various reaction conditions in the presence of chloride. These results indicate how the chloride ion strongly competes with water in the ring opening of epoxide.

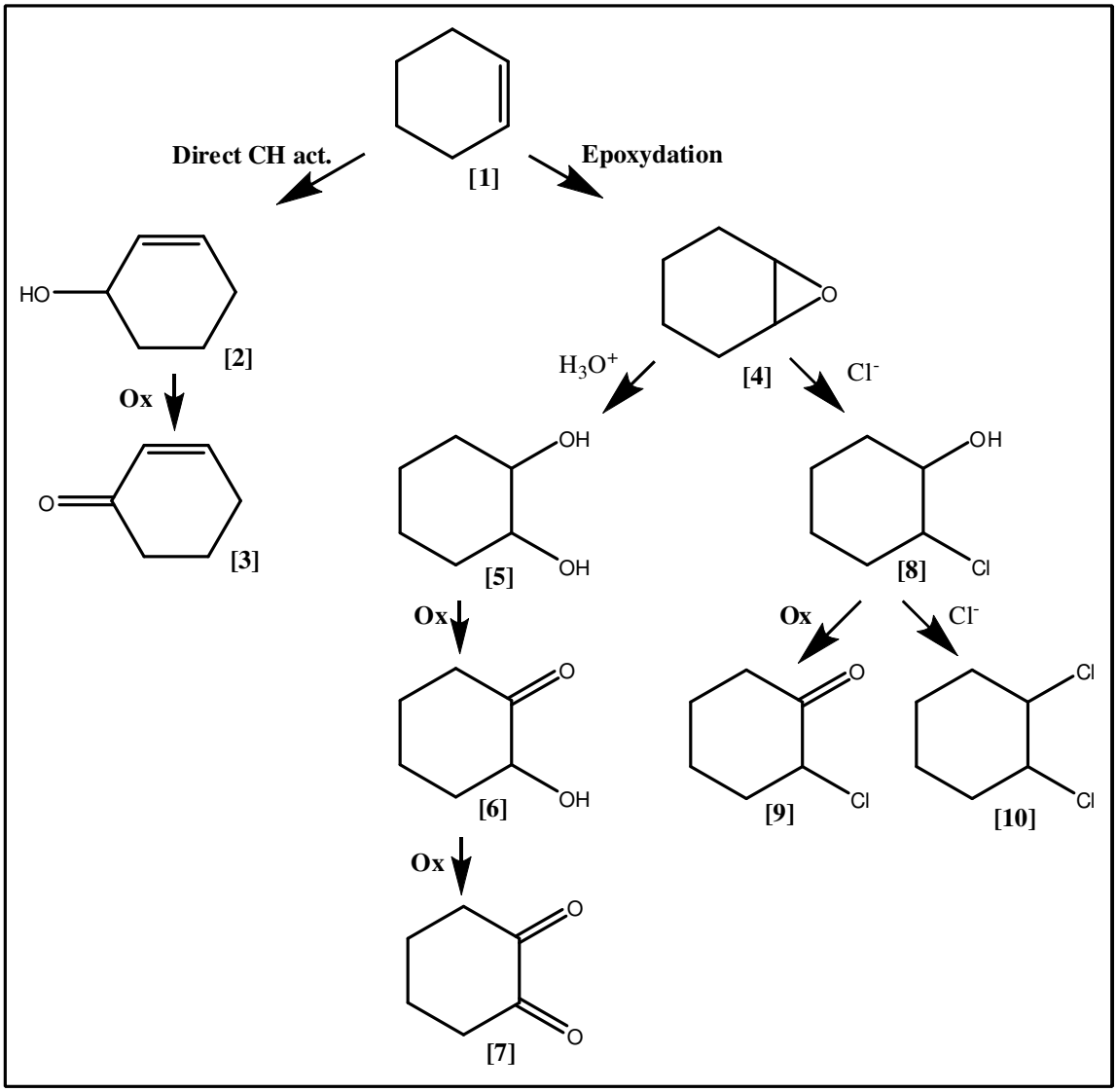


Fig. 1) Products distribution in presence of chloride ion

With refer to Fig. 7 in Chap. 3, we may assert that transformation of [1] to products [3] and [4] is of easy realization. The rate determing step is the oxygen insertion, step [4] → [5], which permits a readily route to adipic acid. The principal goal of cyclohexene transformation into adipic acid was not achieved, because of such a mild oxidative conditions. The substrate was poorly converted and only traces of the desired product were found.

5.3) Halogenations

In this section we exploit the tendency of halogens insertion towards olefin as highlighted by the previous investigations for cyclohexene functionalization.

The halonium ions generation approach has been discussed for the cyclohexene chlorination, where the epoxide formation was followed by nucleophilic attack seems to be more plausible. It was observed how a halogen anion may compete with other nucleophiles to attack and open an epoxyde ring or via halonium ion generation forms an halo-olefin three members ring. The first element which suggests a different behavior along the halogen series is chlorine. The higher reduction potential of chlorine respect to bromine means a more difficult chloronium ions formation. Secondly, chlorine ion is even worse nucleophile which means slower insertion rate into the epoxide ring, justifying the wide products distribution (not observable in the case of bromination). In particular the formation of large percentages of cyclohexen-2-ol and cyclohexen-2-one suggest low reactivity of chlorine, allowing the system to realize C-H oxidation in α position respect to the unsaturation.

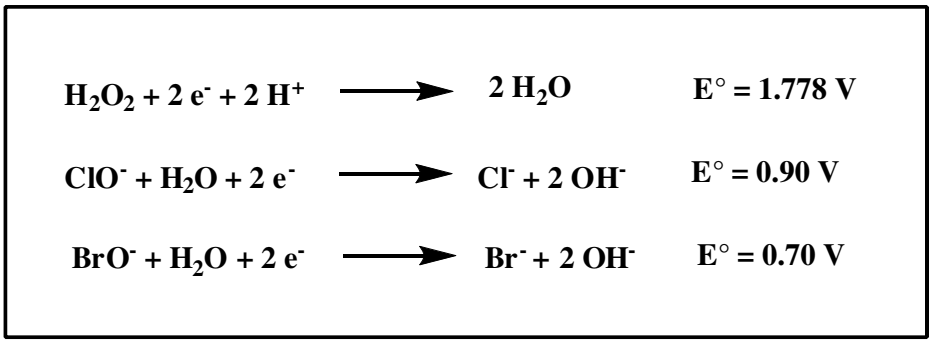


Fig. 2) Halonium species reduction potentials

In **Entry 1** cyclohexane oxidation was carried out in an aqueous buffer solution and Bu_4NCl was used as a phase transfer and as a chlorine source. It is evident that the interaction between the catalyst and the substrate is very poor. Only one half of the converted substrate go through epoxide formation to give mainly the dichloro product, due to the large availability of halogen ions. The other half go to cyclohexen-2-one. In **Entry 2** the adoption of CH_3COOH in MeCN for ensures protons availability and allows to rise the conversion up to 70% with the chlorohydrins as main product. However it is not possible to achieve high selectivity levels, as the chlorine reaction pathway remains very slow, in particular if compared to the bromination results in similar conditions (**Entry 6**). A biphasic solution was studied in **Entry 3** with the aim to improve both the

epoxide generation as well as the ions availability in presence of a tetra-butylammonium salt. The conversion results were slightly improved compared to **Entry 1**, but cyclohexen-2-one was the main product, due to the low reaction temperature, which promote again the faster reaction. In **Entry 4,** MeOH was introduced as a solvent and as a nucleophilic competitor but no methanol insertion was found. This supports the thesis of the epoxide formation versus chloronium ions generation.

Entry	1	2	3	4
Conversion [%]	5	70	20	30
2-Chlorocyclohexanol	10	58	4	53
Cyclohexene-2-one	45	36	64	35
1,2-Dichlorocyclohexane	45	6	32	12
1,2-chlorometoxy Cyclohexane	x	x	x	0

Table 3) Chlorohydroxylation experiments GM-MS % results

Entry	5	6	7	8
Conversion [%]	97	37	38	95
Cyclohex-2-enone	2	2	1	2
2-Bromo Cyclohexanol	0	0	0	9
1,2-dibromo Cyclohexane	88	98	22	19
1,3/1,4-dibromo Cyclohexane	10	0	0	0
1,2-bromometoxy Cyclohexane	0	0	77	70

Table 4) Bromohydroxylation experiments GM-MS % results

It is well know that tungstate exchanged on naturally occurring minerals such as hydrotalcite- and takovite-like material has been demonstrated to be an excellent mimic for haloperoxidases[87]. It is reasonable that olefins bromo-hydroxylation goes through a similar catalytic cycle such one proposed for the takovite catalyzed oxidative transformation[88] (Fig. 3), involving iron oxo- and peroxo-species for the bromonium ions generation. The high reactive species does a first electrophilic attack on the olefin. This is followed by a nucleophilic attack by HO^-, Br^-, RO^- species to give the corresponding products.

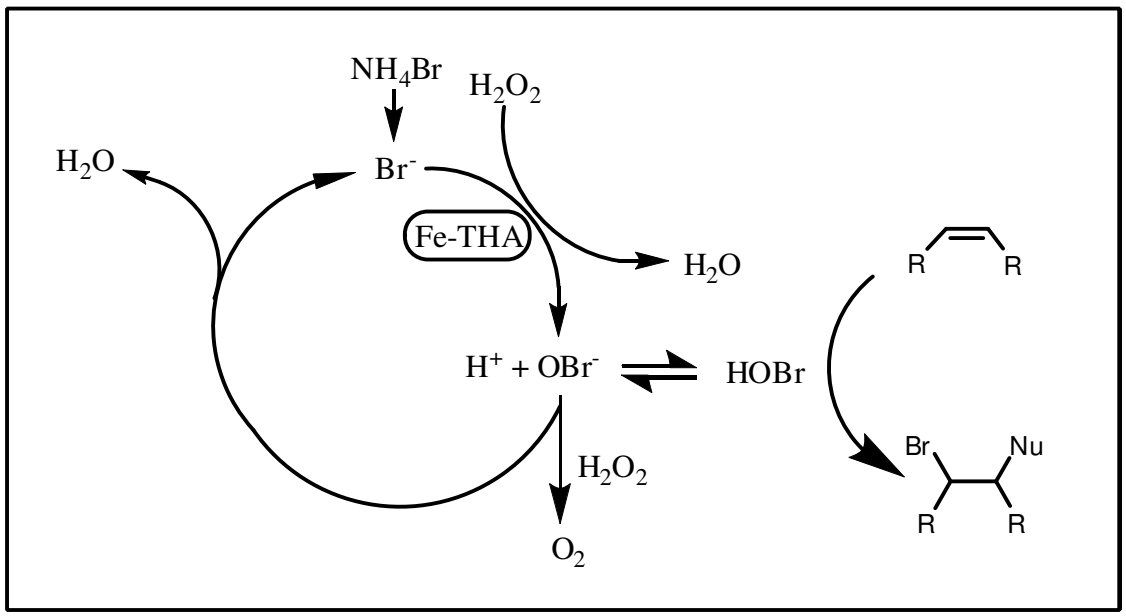


Fig. 3) Proposed Bromohydroxylation sche

In **Entry 5** the bromine concentration in $MeCN/CH_3COOH$ solution is high and the reaction seems following the proposed mechanism. The main product is the dibromo specie. The bromine source Bu_4NBr was chosen to guarantee the miscibility of all phases and to improve the mixing between ions in an organic environment, but the substitution with the cheaper NH_4Br did not affect considerably the reactions results. The use of NH_4Br is preferable, in particular from the atom efficiency point of view but the influence of the generated ammonia during the reaction on the pH has to be investigated.

In **Entry 6** the ammonium bromine salt and the oxidant were mixed together to facilitate the bromonium formation and afterwards added rapidly into a diluted reaction mixture at room temperature. As expected the conversion fall down but the system tends totally to the dibromo product, meaning that bromonium species formation is still very easy and bromine shows great nucleophilic activity.

If a nucleophile competitor as MeOH is introduced as a solvent (**Entry 7**) the result as expected is a mixture of 1,2-dibromocyclohexane and metoxy substituted product, 1,2-bromo-metoxycyclohexane. MeOH in large quantity strongly compete with the others nucleophilic species in opening the bromonium tree-atom ring. A better tuning of the reaction conditions (**Entry 8**) brings to almost full cyclohexane conversion, but unfortunately it was not possible to guarantee the same selectivity as before. Higher temperature is needed to enhance the reaction rate and to get full conversion in only one hour, also the larger amount of oxidant used help in this goal and at the same time dilutes the bromine source. The last entry is the only one where bromohydrins have been observed in appreciable amounts, due to the large volume of water introduced with the oxidant. Methanol as well can undergoes an oxidation but the energy needed for the C-H proton abstraction is too high for the catalytic system; no methanol oxidation products were found. Bromohydrins can undergoes an attack by bromonium species to give the corresponding α-bromoketones[89]. In all investigated reaction conditions no α-bromoketones were found, suggesting that further attacks don't take place (Fig. 4)

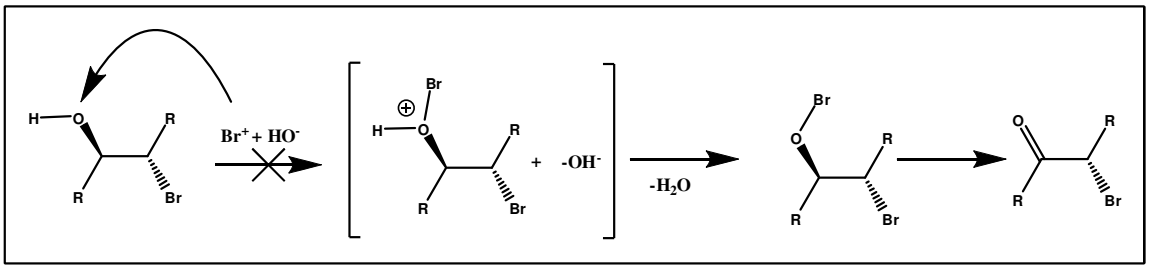


Fig. 4) α-Bromoketones formation

6) Conclusions

A large number of oxidative catalysis screening has been carried out with two distinctive iron systems: $[Fe(phen)_2Cl_2]NO_3$ and the in-situ formed Fe-THA catalyst.

Common eco-compatibile reaction conditions imply the use of low temperatures and mild reactants as H_2O_2 or halide salts as a halogens sources.

- The Iron-Phenantroline complex $[Fe(phen)_2Cl_2]NO_3$ was synthesized and fully characterized by UV spectroscopic analysis and by X-ray diffraction analysis. The N-coordinated complex was chosen to affords selective alcohol oxidation, in mild optimized conditions by using an eco-friendly environment and hydrogen peroxide as oxidant, providing high TOF values and great selectivity. The oxidative mechanism probably involve the formation of Fe^{V}=O species which has the key role in the oxidation.
- The Iron-THA in-situ complex was used as catalyst for alcohols oxidation, exhibiting a satisfying activity. The proposed oxidation mechanism, based on recent literature papers implies the formation of transient oxo-hydroxo-iron^{V} species in the hydrogen peroxide catalytic cycle. ArgusLab molecular modelling software fits the coordinative mode of THA towards iron centre as distorted octahedral cationic complex. The inter-ring hemilabile ketone oxygen might assist the vacant coordinative site, stabilizing the entire structure by Van der Walls interactions.

In both catalytic systems, the choice of a pH 1 buffered aqueous environment results a key factor in enhancing the activity.

- The catalytic ability of the Iron-THA in-situ complex has been also investigated in oxidative C-H activation, showing some promising results with substrates as cyclooctane and cyclohexane.
- Cyclohexene oxidation was further explored with the aim of getting direct conversion to adipic acid. Unfortunately, the Fe-THA system seems not to be able to succeeded in oxygen insertion under the experimental conditions, giving epoxide hydrolysis compounds as main products.
- Cyclohexene was also studied in oxidative halogenations, catalyzed by Fe-THA in presence of halide salts and H_2O_2. The cyclohexene is transformed to the useful 1,2-chloro-cyclohexanol and 1,2-metoxy-bromocyclohexane although with poor selectivity.

Summarizing,

1. Highly efficient and selective alcohol oxidation has been realized with a new Iron-phenantroline catalyst
2. New possible applications of the Iron-THA system were explored in alcohol oxidation and in oxidative C-H activation,
3. THA has revealed to be a very versatile stabilizing ligand for high valent iron active site.

7) Future perspectives

To confirm the action of the Fe-THA system as catalyst in aqueous acidic media, supplementary monitoring control of pH variation in reaction environment will be useful to collect novel elements for understanding the role of the protons availability upon catalyst activity.

Moreover, further investigations by:

- variable-temperature mass spectroscopy,
- UV spectroscopy,
- cyclic voltammetry
- ^{1}H and ^{13}C NMR, either in solution or in solid state,

to intercept the intermediates and to identify the nature and the role in the speculated reaction profile are needed.

Ultimately:

- recognition of a defined molecular weight and isolation of the pre-catalyst compound or of the presumable active catalyst
- studies in solution or in solid state

would provide clarifying insights to complete comprehension of the system.

- THA ligand can be modified with the insertion of chiral functionalities to hopefully induce asymmetric oxidative transformations.

8) Appendix

Products mass fragmentation

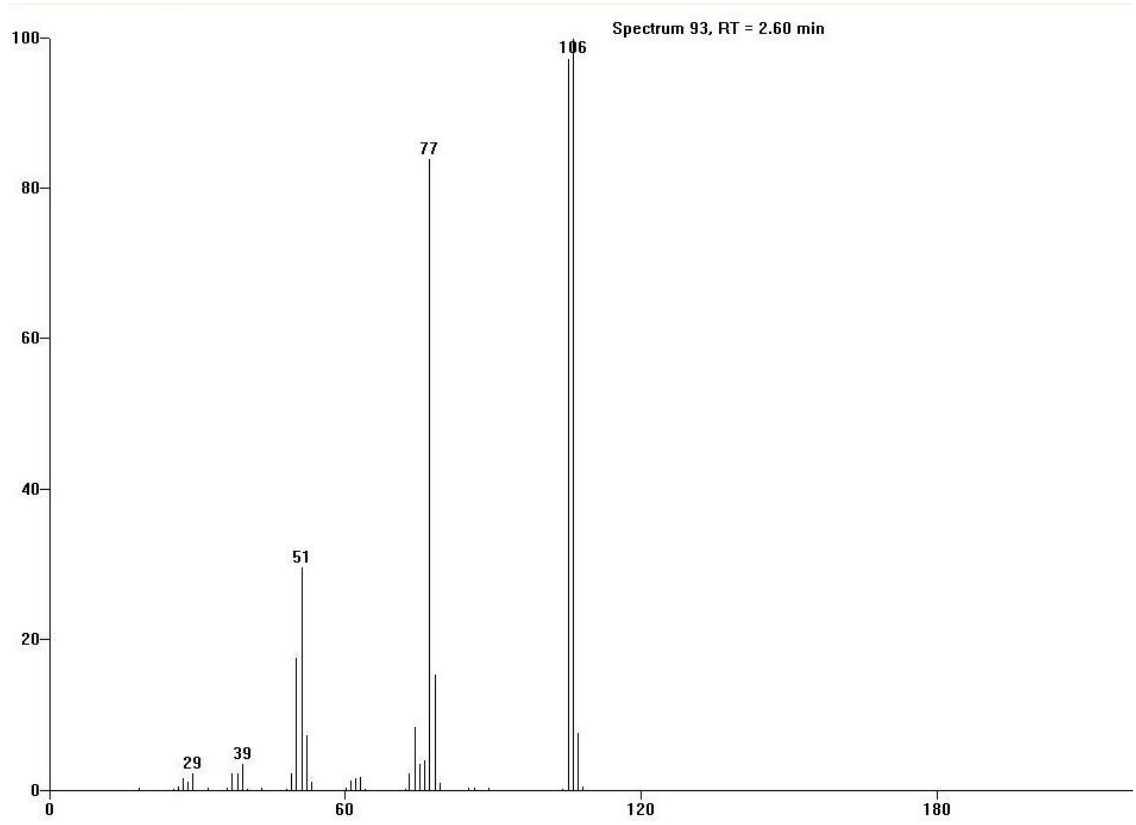


Fig. 1) Benzaldehyde

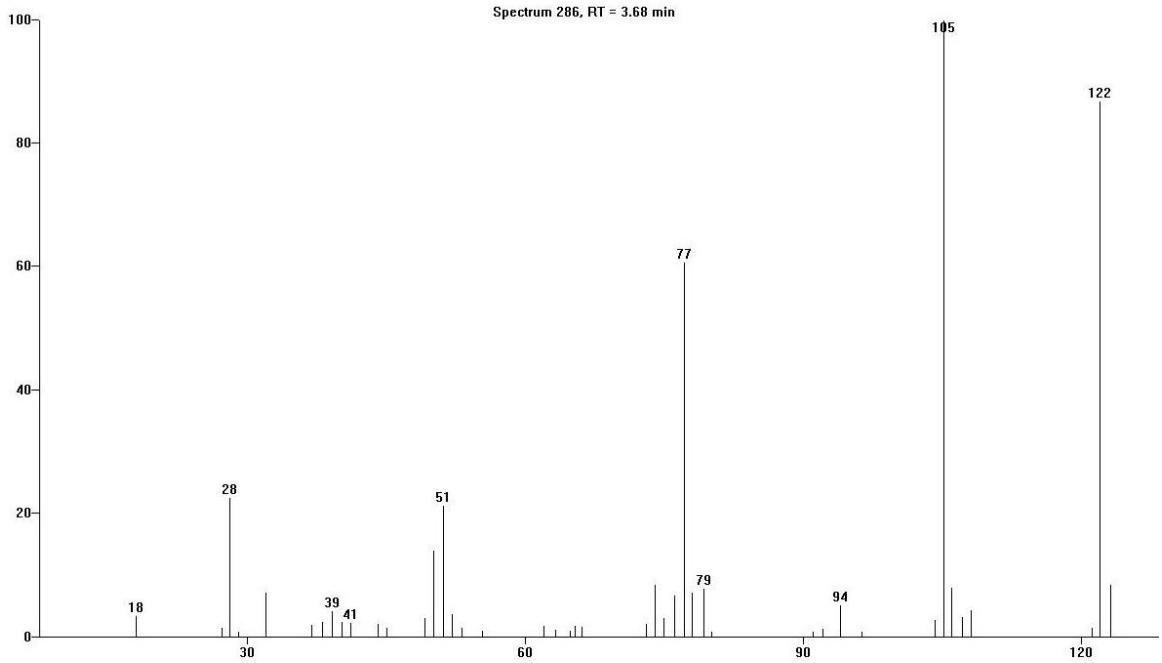


Fig. 2)Benzoic acid

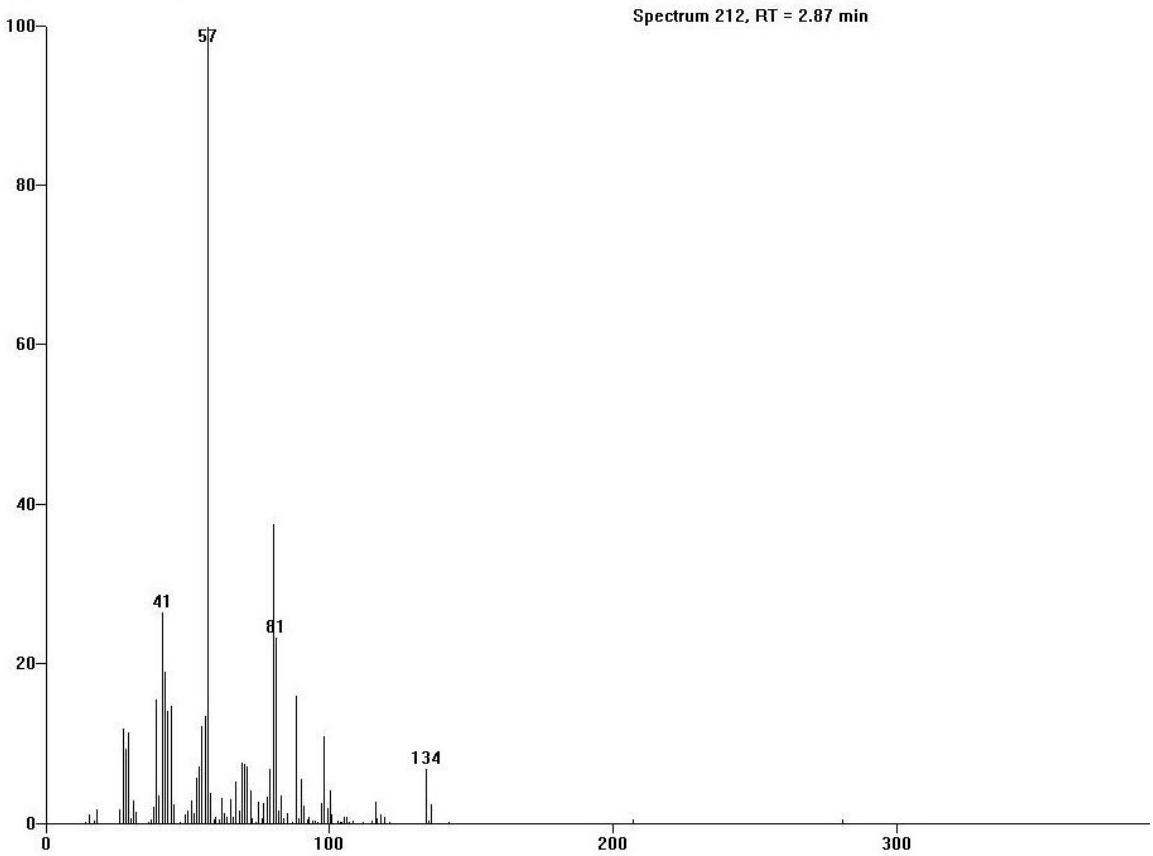


Fig. 3) 1,2-Chlorocyclohexanol

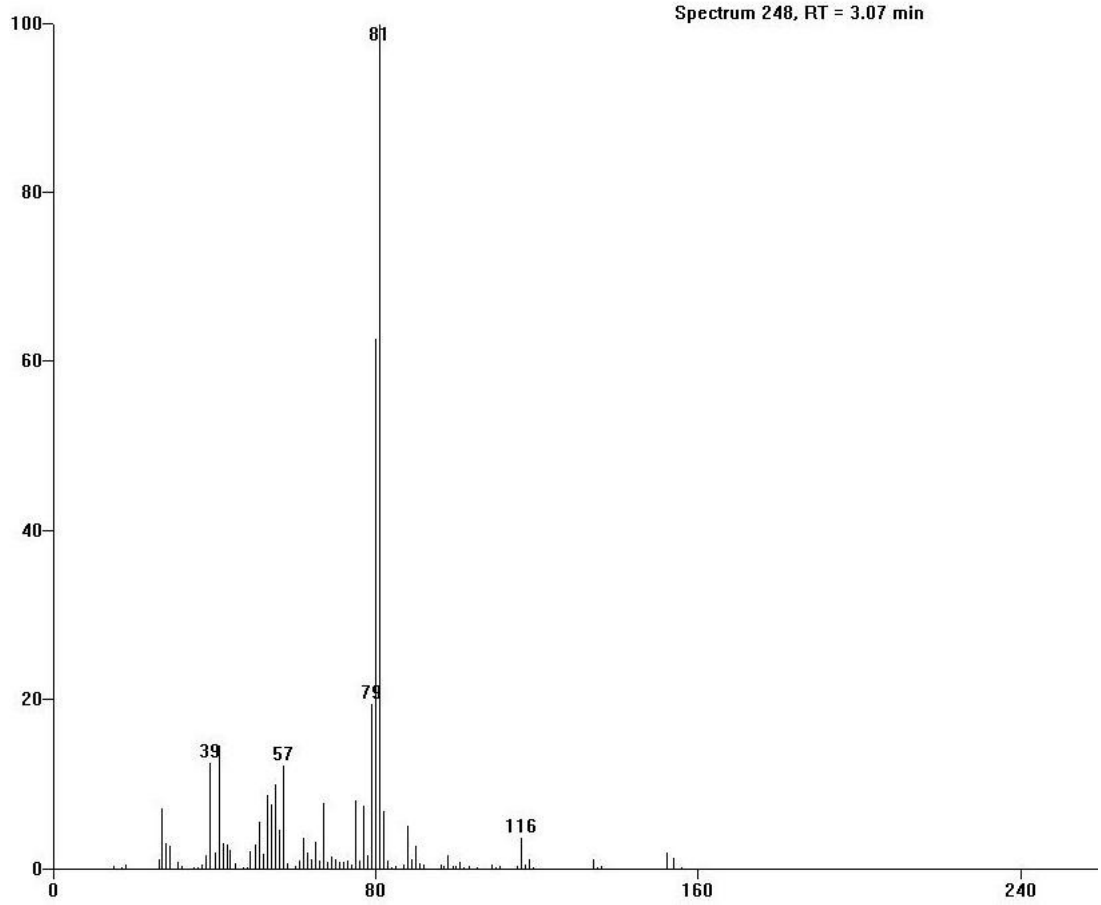


Fig. 4) 1,2-dichloro-cyclohexane

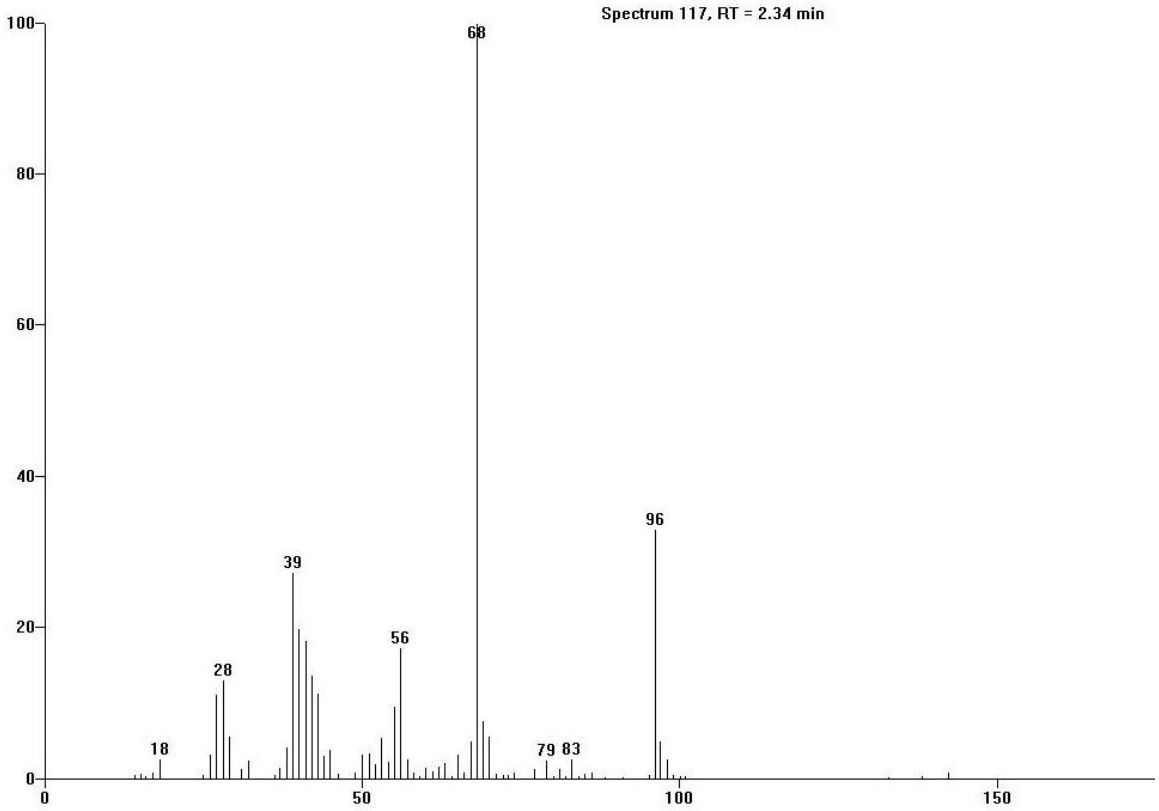


Fig. 5) Cyclohexene-2-one

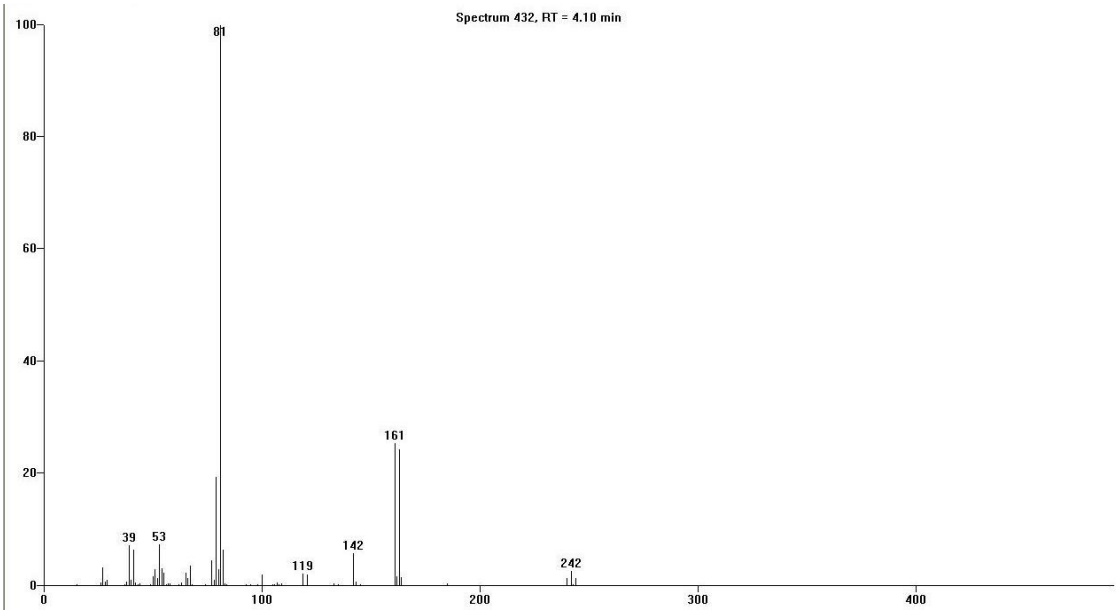


Fig. 6) Dibromo cyclohexane

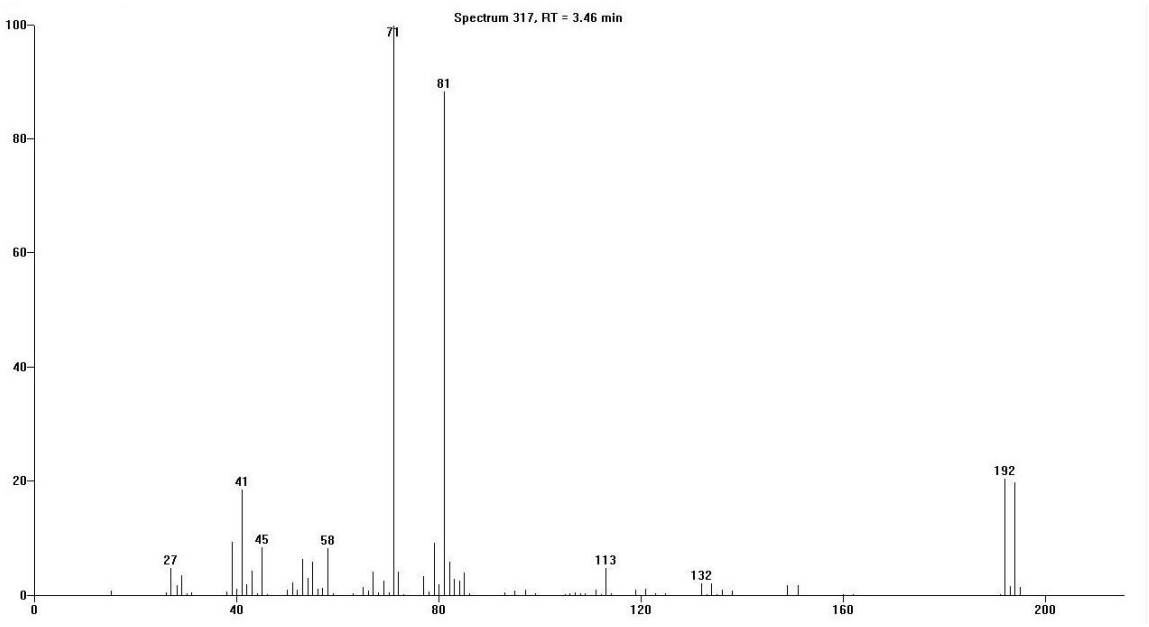
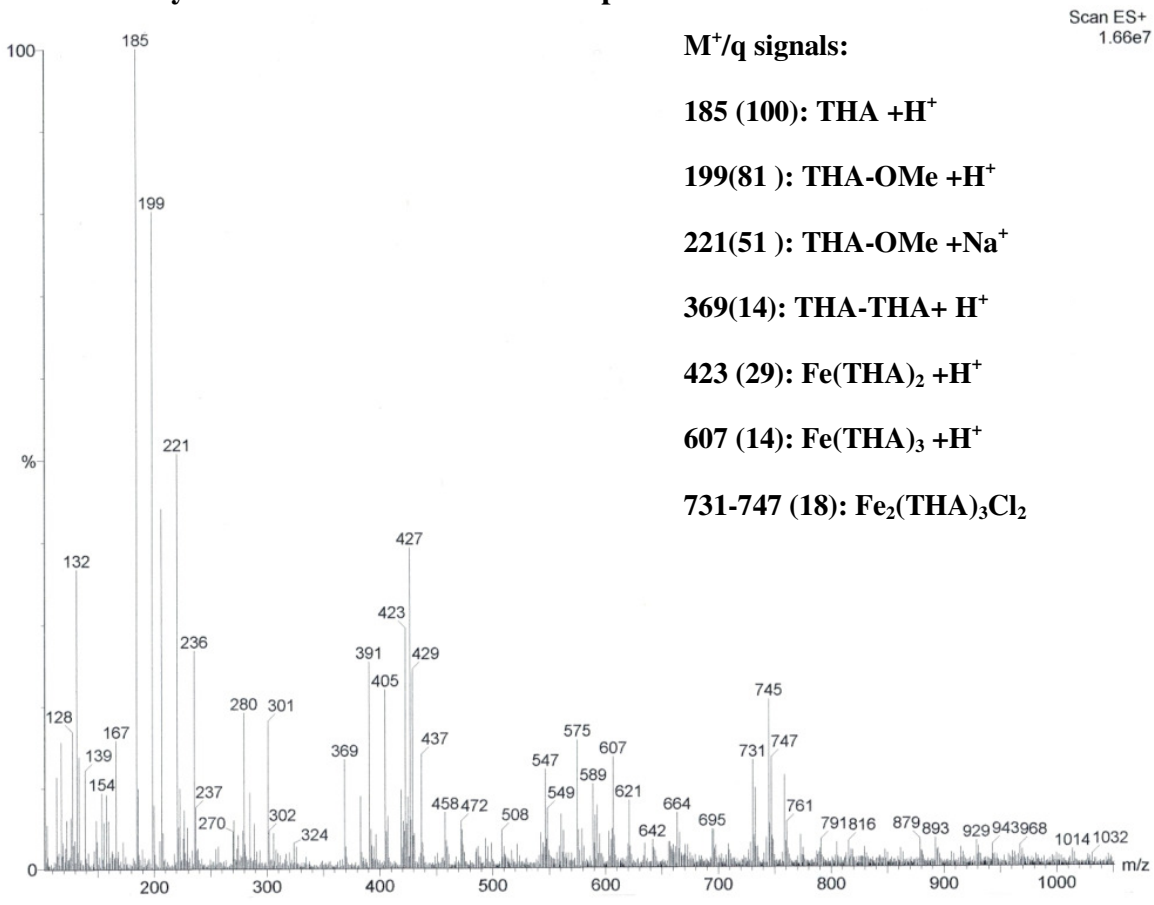


Fig. 7) 1,2-bromo-metoxycyclohexane

MS-ESI analysis of the Fe–THA in-situ complex



M^+/q signals:

185 (100): THA $+H^+$

199(81): THA-OMe $+H^+$

221(51): THA-OMe $+Na^+$

369(14): THA-THA+ H^+

423 (29): $Fe(THA)_2$ $+H^+$

607 (14): $Fe(THA)_3$ $+H^+$

731-747 (18): $Fe_2(THA)_3Cl_2$

Fig. 8) MS-ESI$^+$ of the Fe–THA in-situ complex in solution of MeOH, relatives percentage in parenthesis.

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